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

Introduction

On April 1, 2008, in the National Vaccination Program (RVP) Triaxis-Polio® of SP MSD, the DaPT-IPV (Diphtheria, Acellular Pertussis, Tetanus and Polio) booster vaccine that until then was administered at 4 years of age, was replaced by Infanrix-IPV® of GSK [1]. Until 2011, Adverse Events Following Immunisation (AEFIs) to RVP vaccinations were monitored by the National Institute for Public Health and the Environment (RIVM). In the second half of 2008, the RIVM noticed a sharp increase in the number of reports of local reactions after administration of the DaPT-IPV vaccine (Infanrix-IPV®) at 4 years of age. The vast majority of these reports involved severe local reactions (> 5cm), sometimes extending over the shoulder and / or elbow joint [2,3]. Extensive local reactions that extend to beyond the adjacent joint are also referred to in the literature as extensive swelling of the vaccinated limb (ELS).
Since 2011, AEFIs of RVP vaccinations have been monitored by Pharmacovigilance Centre Lareb. The annual reports for RVP vaccines show that AEFIs are reported more frequently after administration of Infanrix-IPV® at 4 years of age than after vaccines administered at other vaccination times [4]. The vast majority of these reports are reports of local reactions, of which an important part is about ELS. In the course of 2017 Infanrix-IPV® was replaced by Boostrix-Polio® from GSK. Our hypothesis is that this replacement has led to a decrease in the number of spontaneous reports and in particular to reports of ELS, reactions at the injection site and fever.

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 two 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, the RIVM was requested for an overview of all DaPT-IPV vaccines administered around 4 years of age between 1 January 2011 and 31 December 2017, 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 4 year olds between 1 January 2013 and 31 December 2017 based on data from 'Praeventis' (Praeventis Februari 7, 2018)

Vaccination year	Infanrix IPV®	Boostrix Polio®	DaPT-IPV unknown / other*	Total**
2011	172,983	1	1,528	174,512
2012	172,618	0	1,365	173,983
2013	171,418	0	1,071	172,489
2014	170,605	0	939	171,544
2015	165,788	1	1,249	167,038
2016	158,231	9	1,189	159,429
2017	39,473	116,670	538	156,681
Total	1,051,116	116,681	7,879	1,175,676

*For instance Infanrix hexa® zonder 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 December 2017, Lareb received 2663 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 inflammation, fever and other AEFIs. The vast majority concerns reports of injection site inflammation (n=1367) and reports of ELS (n=727) whether or not in combination with fever. The number of reports of fever without injection site inflammation / ELS (n=260) and other AEFIs (n=309) is limited.

Reporting Rate

After replacing Infanrix-IPV® with Boostrix polio® in 2017, the reporting rate of the total number of reports dropped from 49.7 (range 15.7 – 49.7) to 14.7 per 10,000 vaccinated children. In particular, the reporting rate of ELS dropped from 10.6 (range 4.3-10.6) to 1.0. The reporting rate also decreases for the other AEFIs, such as injection site inflammation, fever and other AEFIs, but to a lesser extent. See table 2.

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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 2011 to 31 December 2017. The numbers between () is the reporting rate per 10,000 administered vaccines

	2011		2012		2013		2014		2015		2016		2017		
vaccine	**Inf. IPV**	**Boostr.P.**	**Inf. IPV**	**Boostr.P.**	**Inf. IPV**	**Boostr.P.**	**Inf. IPV**	**Boostr.P.**	**Inf. IPV**	**Boostr.P.**	**Inf. IPV**	**Boostr. P.**	**Inf. IPV**	**Boostr.P.**	**total**
Administered vaccines	172983	1	172618		171418		170605		165788	1	158231	9	39473	116670	
Total N reports	**290 (16.8)**		**407 (23.6)**		**334 (19.5)**		**268 (15.7)**		**429 (25.9)**		**567 (35.8)**	**1**	**196 (49.7)**	**171 (14.7)**	**2663**
Total N ELS	**101 (5.8)**		**152 (8.8)**		**98 (5.7)**		**73 (4.3)**		**107 (6.5)**		**142 (9.0)**		**42 (10.6)**	**12 (1.0)**	**727**
With fever	*25*		*36*		*27*		*18*		*39*		*52*		*20*	*2*	*219*
ELS without fever	*76*		*116*		*71*		*55*		*68*		*90*		*22*	*10*	*508*
Total N injection site inflammation	**110 (6.4)**		**165 (9.6)**		**168 (9.8)**		**112 (6.6)**		**253 (15.3)**		**330 (20.9)**	**1**	**122 (30.9)**	**106 (9.1)**	**1367**
With fever	*27*		*26*		*40*		*28*		*69*		*110*		*24*	*36*	*360*
Without fever	*83*		*139*		*128*		*84*		*184*		*220*	*1*	*98*	*70*	1007
N Fever	**77 (4.5)**		**100 (5.8)**		**103 (6.0)**		**88 (5.2)**		**137 (8.3)**		**209 (13.2)**		**57 (14.4)**	**68 (5.8)**	**839**
ELS and fever	*25*		*36*		*27*		*18*		*39*		*52*		*20*	*2*	*219*
Injectionsite inflammation with fever	*27*		*26*		*40*		*28*		*69*		*110*		*24*	*36*	*360*
Fever without ELS and injectionsite inflammation	*25*		*38*		*36*		*42*		*29*		*47*		*13*	*30*	*260*
Other AEFIs	**54 (3.1)**		**52 (3.0)**		**32 (1.9)**		**41 (2.4)**		**40 (2.4)**		**48 (3.0)**		**19 (4.8)**	**23 (2.0)**	**309**

Rate Ratios

To investigate possible differences as a result of the switch from Infanrix IPV® to Boostrix Polio®, the further analysis focuses on 2016 and 2017. This is to exclude possible disruptions due to priming differences on the infant's age. All children who were vaccinated in 2016 and 2017 were vaccinated with Infanrix hexa® at infant age and differ only in the administered booster vaccine at 4 years of age. For all reports and for ELS, injection site inflammation, fever and other AEFIs separately, the Rate Ratio of Infanrix-IPV® was calculated in comparison with Boostrix Polio® and the corresponding 95% confidence interval (Addendum 1)

Table 3. Rate ratios in the Lareb database

ATC5/7	MedDRA Preferred term	Rate Ratios [CI]	A	B	C	D
	Alle AEFI	2.62 (2.22-3.10)	763	196941	172	116507
	ELS	9.05 (5.05-16.24)	184	197520	12	116667
	Injectionsite inflammation	2.50 (2.02-3.08)	452	197252	107	116572
	Fever	2.31 (1.77-3.02)	266	197438	68	116611
	Other AEFIs	1.72 (1.07-2.76)	67	197637	23	116656

A= N children vaccinated with Infanrix IPV with AEFI
B= N children vaccinated with Infanrix IPV without AEFI
C= N children vaccinated with Boostrix Polio with AEFI
B= children vaccinated with Boostrix Polio without AEFI

Other sources of information

SmPC

The SmPC of Triaxis Polio®, Infanrix-IPV® and Boostrix Polio® all mention Extensive Limb Swelling (ELS) as an AEFI in 4.8 of the SmPC. [5-7]. The Triaxis Polio® SmPC specifies that the risk appears to be dependent on the number of previous doses of DaPT-IPV vaccine, with an increased risk after the 4th and 5th dose "[5]. The SmPC from Boostrix Polio® states in 4.8: "Data suggests that in individuals vaccinated with DaPT during childhood, a second booster dose may increase local reactions". Furthermore, it is stated that injection site reactions (such as redness and / or swelling), pain on the injection site is very common and extensive swelling of the vaccinated limb (sometimes including the adjoining joint) is common [7].

The vaccines differ in the amount of diphtheria, tetanus and pertussis antigens [5-7] (see Addendum 2). 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 makes a factor of 3 to 10 per component and per vaccine. In addition, the booster vaccines differ in the used adjuvants; Triaxis-Polio® exclusively contains aluminum phosphate, Infanrix-IPV® exclusively aluminum hydroxide and Boostrix Polio® a combination of aluminum phosphate and aluminum hydroxide. In addition, the total amount of aluminum varies from 0.33 mg with Triaxis-Polio® to 0.5 mg with Infanrix-IPV® and Boostrix-Polio®.

Literature and mechanism

On the basis of latency time and course, it is assumed that ELS is not an acute allergic reaction or infection [3]. It is generally assumed that it is a severe inflammatory reaction. On the one hand, it is assumed in the literature 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 [3,8]. 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 [9,10,11].
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 [12]. Existing high tetanus specific Th2 cytokine concentrations are associated with an increased risk of local AEFIs [11]. 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 [11]. 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 [11,13,14]. 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 [15,16].

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 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 [15].

Knuf et al. [17] 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 [17]. Lareb previously published an overview of reports of extensive swelling of the vaccinated limb after DT-IPV NVI® vaccine in 2014. 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 [18].

Discussion and conclusion

The total number of spontaneous reports and the reporting rate per year fluctuates. In the second half of 2008, the RIVM signaled an unexpected increase in the number of strong local reactions / ELS after administration of DaPT-IPV booster vaccine at 4 years of age. Since task of monitoring the RVP vaccination AEFI was transferred to Lareb in 2011, Lareb sees that a relatively large amount of AEFI are reported after administration of Infanrix-IPV® at 4 years of age compared to the other vaccination moments. The majority of these reports concern reports of injection site inflammation and ELS. After the switch from Infanrix-IPV® to Boostrix Polio® in 2017, Lareb sees a sharp decrease in the number of reports. The reporting rate per 10,000 vaccinated people decreased from 49.7 to 14.7. The decrease is most pronounced in the category ELS-reports, where the reporting rate per 10,000 vaccinated people decreased from 10.6 to 1.0, but there is also a decrease in reporting rate in the categories of injection site inflammation, fever and other reports. 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® may be related to differences in composition of the 3 vaccines. Vaccine comparison shows that the amount of diptheria 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. Monitoring provided insight in the reporting pattern of AEFI after a switch in the brand of vaccines used in the RVP and other changes in the RVP.

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Addendum 1.

Calculation Rate Ratio (RR) for the transition from Infanrix hexa to Boostrix Polio over the period 2016 and 2017			
	AEFI	**No AEFI**	**Total**
Infanrix IPV	763	196941	197704
Boostrix P	172	116507	116679
Total	935	313448	
RR	2,62		
95% CI	2,22-3,10		
	ELS	**No ELS**	**Total**
Infanrix IPV	184	197520	197704
Boostrix P	12	116667	116679
Total	196	314187	
RR	9,06		
95% CI	5,05-16,24		
	Injection site inflammation	**No injection site Inflammation**	**Totaal**
Infanrix IPV	452	197252	197704
Boostrix P	107	116572	116679
Total	559	313824	
RR	2,50		
95% CI	2,02-3,08		
	Fever	**No fever**	**Total**
Infanrix IPV	266	197438	197704
Boostrix P	68	116611	116679
Total	334	314049	
RR	2,31		
95% CI	1,77-3,02		
	Other AEFIs	**No other AEFIs**	**Total**
Infanrix IPV	67	197637	197704
Boostrix P	23	116656	116679
Total	90	314293	
RR	1,72		
95% CI	1,07-2,76		

Addendum 2 Comparison of the 3 DaPT vaccines used

	Triaxis-Polio®	**Infanrix-IPV®**	**Boostrix-Polio®**
antigeen	Difterietoxoïd niet minder dan 2 IE* (2Lf)	Difterietoxoïd niet minder dan 30 IE	Difterietoxoid niet minder dan 2 IE (2,5 Lf)
	Tetanustoxoïd niet minder dan 20 IE* (5 Lf)	Tetanustoxoïd niet minder dan 40 IE	Teatnustoxoid niet minder dan 20 IE (5 Lf)
	Kinkhoest antigenen	Kinkhoest antigenen	Bordetella pertussis antigenen
	Kinkhoesttoxoïd 2,5 microgram	Kinkhoesttoxoïd 25 microgram	Pertussistoxoid 8 microgram
	Filamenteus hemagglutinine 5 microgram	Filamenteus hemagglutinine 25 microgram	Filamenteus Hemagglutinine 8 (microgram)
	Pertactine 3 microgram	Pertactine 8 microgram	Pertactine 2,5 microgram
	Fimbriale agglutinogenen 2 en 3 5 microgram		
	Poliovirus (geïnactiveerd)**	Poliovirus (geïnactiveerd)**	Poliovirus (geïnactiveerd)**
	Type 1 40 D-antigeeneenheden	Type 1 (Mahoneystam) 40 D-antigeeneenheden	Type 1 (Mahoneystam) 40 D-antigeeneenheden
	Type 2 8 D-antigeeneenheden	Type 2 (MEF-1 stam) 8 D-antigeeneenheden	Type 2 (MEF-1 stam) 8 D-antigeeneenheden
	Type 3 32 D-antigeeneenheden	Type 3 (Sauketstam) 32 D-antigeeneenheden	Type 3 (Sauketstam) 32 D-antigeeneenheden
adjuvans	Aluminiumfosfaat 1,5 mg	Aluminiumhydroxide (Al(OH)3)	geadsorbeerd aan gehydrolyseerd alumiumhydroxie en aluminiumfosfaat
	(0,33 mg als aluminium)	totaal Al^{3+} 0,5 milligram	totaal Al^{3+}+ 0.5 mg
emulgator	Polysorbaat 80		
conserverveermiddelen	Fenoxyethanol		
reststop	Formaldehyde	Natriumcloride	Natriumchloride
	Glutaaraldehyde	Medium 199 (aminozuren, mineraalzouten, vitaminien)	Medium 199 (als stabilisator met aminozuren, mineraalzouten, vitaminen en andere bestanddelen)
	streptomycine		Water voor injectie
	neomycine		
	polymyine B		
	bovien serumalbumine		
stopper	latex vrij		

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