Overview of reports of extensive swelling of the vaccinated limb (ELS) after DTP NVI® vaccine

Introduction

In the Netherlands, children receive a booster vaccination against diphtheria, tetanus and polio (DT-IPV) and the second vaccination against mumps, measles and rubella as part of the Netherlands Immunisation Programme at the age of about 9 years. The vaccines that are currently used are DT-IPV NVI® and MMRVaxPro®. The vaccines are administered at the same moment in different upper arms.

Injection site inflammation can occur after vaccination and is defined by Lareb as at least two symptoms out of swelling, redness, warmth, pain or decreased function. Sometimes the inflammation extends over the joint or the inflammation is located around the vaccinated limb. This adverse drug reaction (ADR) is known as extensive swelling of the vaccinated limb (ELS) [1].

Since spring 2013 Lareb found an increase in the number of reports of ELS after DT-IPV vaccination at the age of 9 years. A similar increase of major inflammatory injection site reactions following DTaP-IPV vaccination at the age 4 was also noted by the RIVM from 2008 [2-3]. It is striking that the changes in the pattern in this particular adverse event following immunisation seem to occur in the same birth cohort. A possible explanation might be that changes in patterns of ADR's following vaccination may be the result of changes in the Netherlands Immunisation Program in the past. The increase in 2008 of strong local inflammatory responses after the DTaP-IPV vaccination at the age of 4 years and the increase in 2013 after the DT-IPV vaccination at the age of 9 years could indicate that ELS is associated with the vaccine changes in infancy in 2005, when the whole cell pertussis vaccine was replaced by acellular pertussis vaccine. It could also be the result of the introduction of new vaccines in the past and be associated by carrier proteins of the conjugated vaccines, the adjuvants or the preservatives in these new vaccines.

Reports

On October 1st 2013, the database of Netherlands Pharmacovigilance Centre Lareb contained 15 cases of ELS after DTP-IPV vaccination, of which 13 cases were reported in 2013. Their vaccination history is shown in Table 1.

The children were born between May 2003 and December 2004, the majority was born in 2004. One child was born in 2000. Two children started there vaccination programme outside the Netherlands, one in Italy (child G) and one in China (child J). All but one child were male.

Seven children had a regular Dutch vaccination schedule, with the vaccines that were then current, a regular age of start of the vaccination programme and with normal intervals between the vaccinations. Five children had a different schedule, because they started abroad or because the parents have chosen for different vaccines, with a later start or with different interval between the vaccinations. Four children started with whole cell pertussis vaccine and finished with acellular pertussis vaccine. From the children started abroad it is not known if they started

with whole cell pertussis vaccine. Child A never received a vaccine containing pertussis and all the vaccines contained a low dose of diphtheria toxoid.
All but one (child J) had a Hib vaccine. Four children had Hepatitis B vaccine. The total doses aluminium adjuvanted vaccines varies between six and ten doses.

In three of the cases it had been reported that after the DTaP-IPV vaccination at age 4 years, a similar reaction had occurred. In one case it was reported that the swelling after the DTaP-IPV vaccination at the age of 4 years was larger than the swelling after the DT-IPV vaccination at the age of 9 years.

The latency period between vaccination and the onset of ELS was 4 to 27 hours, averaging 16 hours. The most commonly reported additional systemic symptoms are headache and pyrexia.

Table 1. Vaccination history of the children with ELS

Pat. Age sex	Scheme			Diphtheria	Pertussis	Tetanus	Hib	Hep.B	Men C	Tetanus carrier	Doses aluminium adjuvanted vaccines
	S	V	I							doses	
A 8-10 years M	L	A	A	dddddd		TTTTTT	HHH			3	6
B 8-10 years M	N	N	N	DDDDDd	WWWAA	TTTTTT	HHHH		M	5	7
C 8-10 years F	N	N	N	DDDDDd	AAAAA	TTTTTT	HHHH		M	5	7
D 8-10 years M	L	N	A	DDDDDd	AAAAA	TTTTTT	HHHH	HHH	M	5	10
E 8-10 years M	N	N	N	DDDDDd	WAAAA	TTTTTT	HHHH		M	5	7
F 8-10 years M	N	N	N	DDDDDd	WWWAA	TTTTTT	HHHH		M	5	7
G 8-10 years M	N	N	A	?????d	?????	?????T	????	???		?	?
H 8-10 years M	N	N	N	DDDDDd	AAAAA	TTTTTT	HHHH		M	5	7
I 8-10 years M	N	N	N	DDDDDd	AAAAA	TTTTTt	HHHH		M	5	7
J 8-10 years M	L	A	A	???Dd	???A	???TT		????	M	?	?
K 8-10 years M	L	A	A	DDDDDd	WWWAA	TTTTT	HHHH			3	6
L 8-10 years M	N	N	N	DDDDDd	AAAAA	TTTTTT	HHHH	HHH	M	5	10

Vaccination scheme of the included cases and lifetime doses Tetanus carrier and aluminum adjuvanted vaccines. Polio and MMR are excluded from the table.
Child G started in Italy and child J started in China. Child C is female.

Scheme:	S=start vaccinations: Late or Normal
	V= vaccine: Abnormal or Normal
	I=intervals: Abnormal or Normal
Diphtheria:	d: ≥5IE; D: ≥30IE (d=2,5Lf, D=15Lf)
Pertussis:	W=whole cell Pertussis; A=acellular pertussis;
?:	used vaccine is unknown

Other sources of information

SmPC

According to the SmPC of DT-IPV NVI®, injection site ADRs are a common event, especially injection site pain, injection site swelling, injection site redness and injection site induration. Extensive swelling at the injection site is very rare. According to the SmPC it occurs in less than 0.1 % of vaccinees [4].

Literature

In the Netherlands the RIVM reported an increased number of minor and major inflammatory injection site reactions following DTaP-IPV vaccination at the age of 4 years from 2008. The majority of these cases are male [2-3].

Based on 497 reported cases to the Vaccine Adverse Events Reporting System (VAERS), collected between 1 July 1990 and 16 January 2003, Woo et all concluded that post vaccination ELS can involve both the proximal and distal segments of the extremity and affects all age groups [5]. ELS was defined as any report of edema extending at least to the elbow or knee of a vaccinated extremity. Of the cases under 18 years of age, 37.1% was female. ELS was reported after a broad range of vaccines. Most reported were polyvalent pneumococcal vaccine (PPV), diphtheria and tetanus toxoid and acellular pertussis vaccine (DTaP), tetanus and diphtheria toxoids (Td), diphtheria and tetanus toxoids and pertussis (DTP) and influenza virus vaccine (FLU). ELS was reported more frequently after higher number of DTaP and DTP vaccinations in the same patient than after a lower number, but a consistent pattern in dose number could not be identified.

In a US investigation ELS occurs after administration of the fourth and fifth booster doses of DTaP vaccines in 2-6% of children given booster doses of DTaP vaccine [6].

In a controlled randomized, evaluator blinded comparison trial of local reactions to DTaP-IPV vaccine and Tdap (a vaccine with a normal tetanus dose and with a lower diphtheria and pertussis dose) booster vaccination, in 4 - 5.5 years-old children, 20% of the children with DTaP-IPV experienced a large local reaction. With Tdap vaccine, such a reactions occurred significantly fewer, but were not eliminated [7].

Mechanism

The pathophysiology of local reactions observed after booster injections is not well known and is probably multifactorial. Marshall *et all.* demonstrated with ultrasound examination edema in both the subcutaneous and muscle tissue spaces in patients with ELS. The fluid accumulation is being greater in the subcutaneous tissue space then in muscle tissue space [1]. Evidence suggests that both antigen and prevaccination immunity may contribute to the development of ELS [6]. Possibly there is a cumulative increased antibody response to several simultaneous administered antigens: diphtheria, tetanus, whole cell and acellular pertussis or to the adjuvants. Some previous studies have shown an association between a severe local reaction and immunoglobulin E antibody levels to the toxoid vaccines and aluminum containing adjuvants [8,9] . In 2012, Lareb reported 10 cases of ELS after seasonal influenza vaccination. The majority (7/10) of these patients were children, who all had a medical history consisting of an immune-mediated disorder, asthma or symptoms of severe allergies [10].

Discussion and conclusions

Since 2008 there has been an increase in the number of reports of injection site reaction / ELS observed in the Netherlands. The increase is mainly due to a substantial increase in local reactions after DTaP-IPV vaccination at the age of 4. Remarkably ELS was increased in preschool children who as infants had a primary series of vaccine containing acellular pertussis or a primary series of mixed whole cell pertussis vaccine and acellular pertussis vaccine.
Since spring 2013 we found an increase in the number of reports of ELS after DT-IPV vaccination at the age of 9 years, the same birth cohort that showed the increase of local reactions in 2008. It concerns almost exclusively male patients. A quarter of the children had also experienced an ELS after the DTaP-IPV vaccination at the age 4 years. The collected data of the vaccination from birth show no consistent pattern. One child never had a vaccine containing pertussis, five children had only acellular pertussis containing vaccines and 4 children had a

mix of whole cell pertussis containing vaccine and acellular pertussis containing vaccine in infancy. One child only had vaccines with a low dose of diphtheria toxoid. All children had aluminum adjuvanted vaccines.

ELS may be an exaggerated inflammatory injection site reaction. Our data of local injection site related reports after vaccination with DT-IPV NVI vaccine at the age of 9 years and after vaccination with DTaP-IPV at the age of 4 years support this assumption. With the increase of ELS there is also a steep increase of local injection site inflammation.

In other countries ELS is also regularly reported following vaccination. Several vaccines are associated with ELS. In particular PPV (polyvalent pneumococcal vaccine), DTaP (diphtheria, tetanus and acellular pertussis vaccine), Td (tetanus diphtheria toxoids), DTP (diphtheria, tetanus toxoids and pertussis vaccine), FLU (influenza vaccine). There is indirect evidence of an increased immune-mediated inflammatory response.

In 2005 the vaccination policy in the Netherlands has changed. Infants were no longer vaccinated with whole cell pertussis vaccine but with acellular pertussis. The increase in 2008 of strong local inflammatory response after the DTaP-IPV vaccination at the age of 4 years and the increase in 2013 after the DT-IPV vaccination at the age of 9 years could indicate that ELS is associated with the vaccine changes in infancy in 2005 in this group of children, but in this small series of case reports, we found no evidence for this theory.
The past 20 years several conjugated vaccines have been added to the Netherlands Immunisation Programme. Several of these vaccines contain tetanus toxoid as a carrier protein: Haemophilus influenzae type b (Hib) vaccine (1993), MenC vaccine (2002), Synflorix (april 2011). With the introduction of these new vaccines into the Netherlands Immunisation Programme the numbers of lifetime doses of tetanus antigen have increased. With the introduction of new vaccines into the Netherlands Immunisation Programme also the numbers of lifetime doses of alum-adjuvants also have increased. The increase of injection site inflammation / ELS the last years could also be related to these changes in the Programme. The increase of ELS after DT-IPV vaccination is an indication for further investigation, with appropriate control groups. Further research should focus on the contributory role of earlier vaccinations in these children and the role of carrier proteins of the conjugated vaccines, adjuvants and other constituents. Such research may elucidate an etiological mechanism for this particular inflammatory reaction.

- Further investigation of the increase of ELS after DT-IPV vaccination is advised

References

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This signal has been raised on May 2014. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).