Injection site abscesses after administration of Infanrix hexa® and synflorix® at infant age.

Introduction

The Netherlands Pharmacovigilance Centre Lareb has received regularly reports of injection site abscesses after administration of Infanrix hexa® and or Synflorix® at infant age. The cause of injection site abscesses is not always clear.

According to the Brighton Collaboration an abscess at an injection site is a localized soft tissue collection [1]. It is a rare local reaction. The term “sterile abscess” has been used imprecisely in the literature, covering settings where no (or an inadequate) evaluation was performed to exclude an infectious aetiology, or where the abscess was pre-treated with antibiotics prior to attempts at culture. By the time drainage is performed on an abscess, a prolonged inflammatory reaction may have occurred precluding the recovery of organisms. In addition, the literature also uses the term “sterile abscess” to describe an inflammatory delayed-type hypersensitivity reaction to one or more components of the vaccine, although limited data were found in the literature to support this aetiology [1].

The Netherlands has an extensive National Immunisation Programme to protect children against infectious diseases. The programme includes vaccination against 12 potentially fatal infectious diseases. During the first year of life infanrix hexa® is given 4 times, usually in combination with Synflorix®. The Synflorix® schedule for infants has been changed in 2014 from a schedule of four vaccinations into a schedule of three vaccinations. Since then at the 2nd vaccination moment only Infanrix hexa® is administered.

The Dutch vaccination protocol determines that when different vaccines are to be administered simultaneously, they will have to be injected in different limbs, in infants usually in the upper legs. As it is often not clear to the reporter what vaccine has been administered in which limb and there is no national policy on administration of vaccine and vaccination site, in case of doubt both vaccines are considered as suspect. If it is clear whether the abscess has appeared at the injection site of the Infanrix hexa® or at the injection site of Synflorix®, then the appropriate vaccine will be considered as suspect and the other vaccine as concomitant.

Based on contracts with vaccine suppliers and/or on the advice of the Heath Council, vaccines in the Netherland Immunisation Program are sometimes substituted. To ensure that in this overview the reported injection site abscess has been caused by Infanrix hexa® or Synflorix®, only injection site abscesses were included, reported between January 2012 and July 2017 and if the vaccines has been administered in infants after January 1, 2012. Information from these reports was collected on administered vaccine(s), vaccination moment (vaccination schedule number), vaccination side, age and sex, latency, duration, diagnosis and treatment, recurrence, source of the report and medical history of the patient.

Reports

Between January 1, 2012 - July 5, 2017 the Pharmacovigilance Centre Lareb received 36 reports of one or more injection site abscesses after administration of Infanrix hexa® and or Synflorix® in infants. Appendix 1 provides an overview of all reports. Of the 36 reports there is one duplicate report (report X and Y). This analysis therefore relates to 35 unique reports, with in total 40 injection site abscesses. In five cases an injection abscess at both injection sites was reported. Most reports are well documented.

In 29 out of 35 reports information of the administered vaccine at the injection site of the abscess was available (83%). In 5 out of these 29 reports (17%) was reported that a bacterial pathogen could be cultured of the content of the injection site abscess (cluster 1). In 2 out of 29 reports no bacteria could be cultured (cluster 2). In the remaining 22 cases it is unknown whether a bacterial pathogen has been detected, because the content of the abscess was not cultivated and or the results of the culture has not been reported (cluster 3). Table 1 provides an overview of 29 reports with known information about the administered vaccine at the injection site of the abscess per cluster.

Table 1 Results of all reports of injection site abscesses received between January 1, 2012 and July 5, 2017 with known information about the administered vaccine at the injection site (N=29): total and per cluster.

	total	Cluster1 Culture: positive	Cluster 2 Culture: negative	Cluster 3 Not cultured or unknown
number of cases	29	5	2	22
Source				
Professional	22	4	1	17
Consumer	7	1	1	5
Vaccination site				
Infanrix hexa®	23	5	1	17
Synflorix®	1			1
Infanrix hexa® + Synflorix®	5		1	4
Vaccination moment				
1	2	2		
2	5	1		4
3	14	2		12
4	8		2	6
Gender				
female	19	2	1	16*
male	10	3	1	6
Time to onset (days)	1 - 150	7 - 25	7 - 150	1 - 120
Treatment setting				
general practitioner	8			8
outpatient clinic	10	2	1	7
hospitalisation	11	3	1	7
Diagnostic tests				
X-ray	1			1
ultrasound	14**	2	4	8
MRI	2	1		1
leucocytosis	5	4		1***
culture abscess content (positive)	7 (5)	5 (5)	2	
body temperature increased	7	1		6
Treatment				
no treatment (spontaneous drainage)	11 (9)	1 (1)		10 (8)
surgical drainage (+ antibiotics)	12 (6)	4 (3)	1 (1)	7 (2)
aspiration (+ antibiotics)	3 (1)		1	2 (1)
unknown	3			3
Course				
recovered (scar)	15 (3)	4	1 (1)	10 (2)
recovering	11	1	1	9
not recovered	1			1
unknown	2			2
Recurrence	4	0		4
Medical history				
eczema	4	1		3

* 2 patients are identical twin sisters
** 14 ultrasound examinations were performed in 12 patients, in one patient three times
*** In one case of leucocytosis, the content of the abscess was not cultured.

In most reports of injection site abscesses with a known vaccine, the abscess occurred at the injection site of Infanrix hexa® (79%). Only once it was reported that the abscess occurred at the injection site of Synflorix® (3%) and five times it was reported that an abscess occurred at both injection sites (17%). In cluster 1 all injection site abscesses with a known vaccine appeared at the injection site of Infanrix hexa®, in cluster 2 in 50% of the cases and cluster 3 in 77% of the cases.

Most abscesses were reported after the 3rd vaccination moment (48%) or 4th vaccination moment (28%). Two times the abscess occurred after the 1st vaccination moment (7%) and five times after the 2nd vaccination moment (17%). In cluster 2 and 3 injection site abscesses were mainly reported after the 3rd and 4th vaccination moment and none after the 1st vaccination moment. Only in cluster 1, injection site abscesses were reported after the 1st vaccination moment.

Two reports of cluster 2 are of an identical twin. Both had an injection site abscess after the 3rd administration of Infanrix hexa®, one child with a latency of 9 days and the other child with a latency of 4 months (report R and S).

Most injection site abscesses occurred in girls (66%). There is a difference between the clusters. In cluster 3, 16 of 22 patients were girls (73%), whereas in cluster 1 injection site abscesses were reported more frequently in boys (60%).

The time to onset (TTO) varies from minutes to 150 days, but has not been reported consistently. Sometimes the TTO of pain, redness or swelling which appeared shortly after vaccination at the injection site have been reported as a TTO of injection site abscess. Other reports mention as TTO the moment when a swelling at the injection site appeared again, or when the swelling started to increase in size, or the moment that the diagnosis was made by means of additional diagnostics. The reported latency time is usually coded by the assessor of Lareb as TTO. For this reason, the clinical course is more informative than the actual reported TTO. Based on this information most abscesses seem to have developed within a period of one or more weeks after vaccination.

Most patients did not have a period of fever prior to the onset of the injection site abscess or during the injection site abscess (76%). Six patients reported fever, three with a TTO of 1 week or more. One patient reported an increased body temperature on the day after vaccination.
In one case, fever in association with leucocytosis and a positive culture was reported (report W).

Eleven of the 29 patients were hospitalized for treatment for one or more days. In addition, 10 patients were treated on an outpatient basis.

In 13 cases diagnostic imaging was performed, 12 times an ultrasound, twice an MRI and once an X-ray. In one patient of cluster 2, three times an ultrasound scan was performed before the diagnosis of injection site abscess was made. In one patient of cluster 3 an X-ray, ultrasound and MRI were successively performed.

Five times leucocytosis was reported, once in combination with increased CRP. In four out of the five cases of leucocytosis, a bacterial pathogen could be cultivated out of the content of the abscess. In one case of leucocytosis, the content of the abscess was not cultured.

In seven times out of 29 cases it was reported that the content of the abscess was cultured. Two times the culture was negative. Five times a bacterial pathogen could be detected: five times a staphylococcus aureus. In the two reports of an injection site abscess after the 1st vaccination moment, in all cases a bacterial pathogen could be detected.

In three of the 29 reported cases it is unknown whether treatment was initiated. In two cases a “wait and see” policy was reported. In nine cases there was spontaneous drainage of the abscesses. Fifteen times an active policy was conducted (52%). Twelve times the abscess was surgically drained and in 6 cases followed by treatment with antibiotics. Three times the content of the abscess was aspirated, in one case followed by treatment with antibiotics. In two out of these three cases it was reported that the parents had subsequently squeezed pus out of the abscess once or several times.

Of two out of 29 patients the further course of the injection site abscess is unknown. Fifteen patients had recovered at the time of reporting, of which three recovered with sequela (scars). Once it was reported that the patient had not recovered at the time of reporting. The remaining 11 patients were at the time of reporting recovering from the injection site abscess.

Patient BC had an injection site abscess after previous administration of Infanrix hexa® or Synflorix®. Patient BE reported again an injection site abscess after the following administration of Infanrix hexa®, but after the later administration of M-M-RVAXPRO, which contains no adjuvant, occurred no injection

site abscess. Patient Z had an abscess following an previous administration of Hepatitis B vaccine (aluminum hydroxide (Al $(OH)_3$) as adjuvant / adsorbent; total amount AL^{3+} 0.5 mg per dose). Patient H had swellings at the injection site after previous administration of a vaccine. In the three cases of recurrent injection site abscesses or injection site reaction, in none of these cases a bacterial pathogen was detected (cluster 3).

Other sources of information

SmPC
In the Summary of Product Characteristics (SmPC) of Infanrix hexa® and Synflorix® injection site abscess is not mentioned as a possible adverse event following immunisation (AEFI) [2,3].

Infanrix hexa® is a combined diphtheria haemophilus-acellular pertussis-poliomyelitis-tetanus-hepatitis B vaccine, with aluminum phosphate ($AlPO_4$) and aluminum hydroxide (Al $(OH)_3$) as adjuvant / adsorbent. The total amount of AL^{3+} in Infanrix hexa® is 0.82 mg per dose [2].

Synflorix® is a conjugated pneumococcal vaccine, with aluminum phosphate ($AlPO_4$) as adjuvant / adsorbent. The total amount of Al^{3+} in Synflorix® is 0.5 mg per dose [3].

Literature
Until 2011, the reports of AEFIs of the National Immunisation Program of children were collected by the National Institute for Public Health and Environment (RIVM). Between 1994 and 2010 89 reports of injection site abscesses were collected after administration of a vaccine in infants. The reporting rate was less than 1/100,000 vaccinations. Most abscesses could be attributed to DTP-IPV-Hib (Hepatitis B) vaccine and occasional to single Hib, Hepatitis B or pneumococcal vaccine. 63% of the reported injection site abscesses in infants were from girls [4].

Over the period 1994 – 2010, the RIVM observed a slight variation in reporting rate between the four different vaccination moments in infants: 1st vaccination 0.8/100,000; 2nd vaccination moment 0.7/100,000; 3rd vaccination moment 0.9/100,000 and 4th vaccination rate 0.8/100,000 [4]. In 38% of the 89 cases the content was cultured. In two thirds of these cases a pathogen could be detected [4]. This means that in about 25% of the cases a pathogen was detected over the period 1994 – 2010.

It has been suggested in the literature that injection site abscesses can be caused by the adjuvant of the vaccine [5- 8]. Bernier and others described an unexpected increase of injection site abscesses in the United States. This increase was associated with the increase of the amount of aluminium by a factor two to three in the vaccine of one of the vaccine suppliers. The authors suggested that, although the majority of inoculations that led to abscesses were given IM, the higher aluminium content in the vaccine resulted in the introduction of more than usual amounts of aluminium into the subcutaneous tissue, which may have contributed to abscess formation.

Itchy nodules at the injection site after vaccination with aluminium-containing vaccines has been reported previously. Bergfors and others reported 64 children with persistent itching nodules and contact allergy to aluminium after vaccination with aluminium-adsorbed vaccines [6]. Typical finding in these case series were: the long TTO, the duration of years of these nodules and intensified itching during intercurrent infections. Contact allergy to aluminium was demonstrated in 60 out of 63 patients. Out of 25 patients who received a booster dose as planned or with a delay of 1-3 years only two had new itching nodules.

Sterile injection site abscesses have been associated with delayed hypersensitivity reactions (Type IV reaction) after initial sensitization to aluminium during previous vaccinations [9,10,11]. In these case reports, the children had no injection site abscess after the first vaccination with aluminium containing vaccines, but they had injection site abscesses after the later vaccinations of aluminium containing vaccines, and they had no injection site abscess after later administration of MMR-vaccines, which are void of aluminium additives. In these three case reports a hypersensitivity reaction for aluminium could be demonstrated in all cases by means of a positive skin test for aluminium.

Administered vaccination.
Annually in the Netherlands about 680,000 times Infanrix hexa® is administered at infant age. Synflorix® was also administered about 680,000 times annually, but since 2014 this has been about 510,000 times annually.

Mechanism
Injection site abscesses are commonly caused by infection, usually a skin bacteria, such as a staphylococcus aureus. Sterile injection site abscesses can be caused by chronic inflammation with granuloma formation, with secondary abscess formation.

In addition, in the literature it has been suggested that the aluminium of the adjuvant could a role in the process of the formation of sterile abscesses. Both Infanrix hexa® and Synflorix® have an aluminium-containing adjuvant, but the type of adjuvant and the amount of aluminium differs between these vaccines. Infanrix hexa® is a combined diphtheria haemophilus-acellular pertussis poliomyelitis tetanus hepatitis B vaccine, with aluminium phosphate ($AlPO_4$) and aluminium hydroxide ($Al(OH)_3$) as adjuvant / adsorbent. The total amount of Al^{3+} in Infanrix hexa® is 0.82 mg per dose. Synflorix® is a conjugated pneumococcal vaccine, with aluminium phosphate ($AlPO_4$) as adjuvant / adsorbent. The total amount of Al^{3+} in Synflorix® is 0.5 mg per dose [1,2]. By regulation it is determined that in the United States the aluminium content of a vaccine may not exceed 0.85 mg of aluminium per dose if the amount is assayed, 1.14 mg/dose if determined by calculation based on the amount of the aluminium compound that is added [12]. In Europe the limit is 1.25 mg per dose [13].

The total amount of aluminum per dose of Infanrix hexa® is higher compared to Synflorix®. It is possible that this difference contributes to abscess formation at the injection site. It is possible that the monthly administration of Infanrix hexa® at the age of 2 to 4 months and depot formation also contributes to the number of abscesses at the injection site of Infanrix hexa®. Although infanrix hexa® is given intramuscular, could the larger amount of aluminum in infanrix hexa® occasionally may lead unintended to administration of aluminum in the subcutaneous tissue. This could also contribute to abscess formation. However, another explanation for the difference in number of reports between Infanrix hexa® compared to Synflorix® may be that vaccination with Infanrix hexa® comprises an additional procedural step before the vaccine can be administered, thus increasing the risk of an infection.

The fact that abscesses mainly occur only after the third and fourth vaccination moment, could be an indication that sensitization against aluminium occurs during the previous vaccination moments. The difference that these abscesses occur mainly on the arm where Infanrix hexa® was given and less on arm of Synflorix®, could possibly be explained, that aluminium hydroxide leads to sensitization more quickly than aluminium phosphate.

Discussion and conclusion

Between January 1, 2012 and July 5, 2017 Pharmacovigilance Center Lareb received 35 reports of injection site abscesses after administration of Infanrix hexa® and or Synflorix® in infants with 40 injection site abscesses in total, on an annual basis six to seven injection site abscesses. In 29 out of 35 reports information of the administered vaccine at the injection site of the abscess was available (83%). In 97% of these cases (28 out of 29), the injection site abscess occurred at the injection site of Infanrix hexa® and 21% (6 out of 29) at the injection site of Synflorix®. Most injection site abscesses occurred in girls. Our findings over the period January 2012 - July 2017 correspond to the findings of the RIVM over the period 1994 – 2010.

The RIVM found over the period 1994 – 2010 that there was only a slight variation in reporting rate between the four different vaccination moments in infants. In our case series, the differences between the four vaccination moments are more pronounced. In our case series injection site abscesses occurred mainly after the 3rd and 4th vaccination moment (85,7% of the cases).

In our case series in seven (cluster 1 and 2) out of 29 cases the pus was cultured of which in five cultures a bacterial pathogen was detected (17%). In the remaining 22 cases the information about the

culture of pus is missing (cluster 3). Over the period 1994-2010 the RIVM found a positive culture in 25% of the cases. In view of the lack of information about whether or not the content of the abscess has been cultured, it cannot be stated with certainty that all abscesses from cluster 3 are sterile abscesses. But the pattern of this cluster 3 is striking. The abscesses mainly occurred after the 3rd or 4th vaccination moment of Infanrix hexa® and never occurred after the 1st vaccination moment of Infanrix hexa® andin some of these cases recurrence have been reported. Cases of injection site abscesses caused by a bacterium can occur at any vaccination moment, also after the 1st administration.
Injection site abscess often lead to a large number of diagnostic procedures, hospitalization, outpatient treatment or treatment by the GP. Most abscesses are treated as caused by a bacterium, which is common cause of abscesses.. For parents of these young children injection site abscess is a profound experience. From the perspective of post-marketing surveillance, it is important that there is clear national policy about which vaccine is administered to which limb / side.

Recommendations

- Injection site abscess as an ADR is neither mentioned in the SPC of Infanrix hexa® nor the SPC of Synflorix®. This side effect is not covered by the more general term "injection site reaction", which describes reactions that differ in cause, latency and duration. HCP and patients should be informed about this potential ADR.

References

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This signal has been raised on March 9, 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

Appendix 1

SRT ID	Sex, age, source	Suspect Vaccine, injection moment	Concomitant Vaccine/medic.	Suspected adverse drug reactions	Time to onset, action with drug, outcome
A; 139505	F; 7 months; JGZ physician	Infanrix hexa®; Synflorix®; 3		Injection site abscess Both sides	6 weeks recovering
B: 140683	F; 14 weeks; JGZ physician	Infanrix hexa®; 2	Synflorix®	Injection site abscess	8 days recovered
				pyrexia	11 days
C: 140791	F; 11 weeks; paediatrician	Infanrix hexa®; 1	Synflorix®	Injection site abscess	19 days
D: 141440	F; 32 weeks; JGZ physician	Infanrix hexa®; Synflorix®; 3		Injection site abscess	10 weeks; Recovered with sequel
E: 142678	M; 5 months parent	Infanrix hexa®; 3	Synflorix®	Injection site abscess	25 days; recovered
F: 144255	F; 11 months parent	Infanrix hexa®; 4	Synflorix®	Injection site abscess	1 month; recovered
G: 145084	F; 22 months; parent	Infanrix hexa®; 3	Synflorix®	Injection site abscess	19 days; Recovered
				Pyrexia	1 day; Recovered
				Crying	5 hours; recovered
H: 149963	M; 4 months; JGZ nurse	Infanrix hexa®; Synflorix®; 3		Injection site abscess	days; recovering
				pyrexia	2 days; recovered
I: 152241	F; months; JGZ physician	Infanrix hexa®; Synflorix®; 3		Injection site abscess	5 weeks; recovering
J: 156429	F; 11 months; JGZ nurse	Infanrix hexa®; 4	Synflorix®;	Injection site abscess	4 days; recovering
K: 156587	M; 3 months; parent	Infanrix hexa®; 2	Synflorix®;	Injection site abscess	1 day; not recovered
				eczema	days; unknown
L: 159366	F; 4months; JGZ nurse	Infanrix hexa®; 3	Synflorix®; Unknown ointment (eczema)	Injection site abscess	29 days; recovered
M: 161088	M; 4 moths; physician	Infanrix hexa®; Synflorix®; 3		Injection site abscess	3 weeks; recovering
N: 166609	F; 11 months; JGZ physician	Infanrix hexa®; 4	Synflorix®;	Injection site abscess	1 week; recovering
O: 173092	M; 7 months; medical student	Infanrix hexa®; 2		Injection site abscess	2 weeks; recovering
P: 180054	M; 11 months; JGZ physician	Infanrix hexa®; Synflorix®; 4		Injection site abscess	4 days; recovered with sequel
Q: 181427	F; 14 weeks; JGZ nurse	Infanrix hexa®; 2		Injection site abscess	2 weeks; recovering
R: 182490	F; 6 months; general practitioner	Infanrix hexa®; 3	Synflorix®;	Injection site abscess	9 days; recovered with sequel

S: 187041	F; 9 months; General practitioner	Infanrix hexa®; 3	Synflorix®;	Injection site abscess	4 months; recovered with sequel
T: 194204	F; 11 months; JGZ nurse	Infanrix hexa®; 4	Synflorix®;	Injection site abscess	?; recovering
U: 194287	M; 11 months; JGZ nurse	Infanrix hexa®; 4	Synflorix®;	Injection site abscess Fever	1 week; Recovering; 1 week; recovered
V: 198171	M; 4 months; JGZ nurse	Infanrix hexa®; 3	Synflorix®;	Injection site abscess	
W: 199205	M; 17 weeks Specialist	Infanrix hexa®; 3	Synflorix®;	Injection site abscess fever	< 2 weeks; recovered ? recovered
X: 202585	M; 4 months; JGZ nurse	Infanrix hexa®; 3	Synflorix®;	Injection site abscess crying	1 day; Recovered 1 day; recovered
Y 202781	M; 4 months; paediatrician	Infanrix hexa®; 3	Synflorix®;	Injection site abscess crying	1 day; Recovered 1 day; recovered
Z: 204656	F; 15 months; JGZ physician	Infanrix hexa®; 4	Synflorix®;	Injection site abscess	3 weeks; recovered
BA: 211941	F; 2 months JGZ physician	Infanrix hexa®; 1	Synflorix®;	Injection site abscess	1 week; recovered
BB: 217122	M; 4 months; JGZ physician	Infanrix hexa®; 3	Synflorix®;	Injection site abscess	5 hours; recovering
BC: 227030	F; 4 months; JGZ physician	Infanrix hexa®; Synflorix®; 3		Injection site abscess	1 day; recovering
BD: 227491	F; 4 months; JGZ physician	Infanrix hexa®; 3	Synflorix®;	Inject. Erythema Injection site abscess	4 hours; Unknown 2 weeks; unknown
BE: 227633	F; 16 weeks; parent	Infanrix hexa®; Synflorix®; 3		Injection site abscess	3 weeks; recovering
BF: 233448	M; 11 weeks; paediatrician	Infanrix hexa®; Synflorix®; 1		Injection site abscess	2 weeks; recovering
BG: 233449	M; 4 months; paediatrician	Infanrix hexa®; Synflorix®; 3		Injection site abscess	1 week; recovering
BH 241372	F; 13 weeks; JGZ nurse	Infanrix hexa®; 2		Injection site abscess	minutes; recovered
BI: 241394	M; 12 months; parent	Synflorix®; 3	Infanrix hexa®; 4	Injection site abscess	16 days; recovered
BJ: 242501	F; 16 months; parent	Infanrix hexa®; Synflorix®; 4		Injection site abscess	5 months; recovered with sequel