1.1. Petechiae and discoloured leg syndrome following immunisation of young infants

Introduction

Young infants receive four immunisations of DPTP-Hib-hepB and three of Pneumococcus during their first year in the Dutch childhood immunisation program. These vaccines are used for *prophylaxis of diphtheria, pertussis, tetanus, polio and hepatitis B infections as well as pneumococcal infection*.

The currently used vaccines in the program are Infanrix hexa® (DPTP-Hib-HepB) and Synflorix® (10-valent Pneumococcus). Children who were born before August 1, 2011 received Pediacel® (DPTP-Hib) and Synflorix®, children who were born before March 1, 2011 received Pediacel® and Prevenar® (7-valent Pneumococcus). Infanrix hexa® and Synflorix® are given in the current Dutch childhood immunisation program at the age of 2, 3, 4 and 11 months. The number of doses administered per year is depending on the number of new-borns and the vaccination coverage.

Bleeding under the skin or into mucosal membranes is called purpura and may be an innocent finding related to mild childhood trauma but on the other hand may be the presenting sign of a life threatening disease. Purpura can be subdivided based on size into petechiae and ecchymoses. Pinpoint areas (less than 2 mm) of hemorrhage, which are reddish-purple lesions are called petechiae, while larger confluent lesions are referred to as ecchymoses. Ecchymoses are commonly called bruises. In some cases, ecchymoses may be tender or raised. In contrast to other erythematous or vascular skin lesions, purpuric lesions do not blanch when pressure is applied to the skin. Careful evaluation of any patient with purpura is important for early diagnosis and treatment, particularly in children who are ill-appearing [1].

In this context, we also have to mention a syndrome, which is known to possibly occur after young infant vaccination. Discoloured leg syndrome (DLS) is a relatively unknown Adverse Event Following Immunisation (AEFI) of the vaccines administered to young infants in the current Dutch childhood immunisation program. DLS is defined as (sudden onset of) even or patchy red, blue or purple discoloration of the leg and/or leg petechiae with or without swelling. The distribution may be the entire leg, it may be or restricted to the upper or lower leg or feet. The discoloration may be homolateral or even contralateral and may sometimes affect both legs. The pelvic region may also be involved (i.e. trousers form). The discoloration does not radiate from the injection site; as such, it differs from (extensive) local reactions [2].

Petechiae are not mentioned in any of the SmPC's as an AEFI [3-6].
Nevertheless, the Netherlands Pharmacovigilance Centre has received 49 reports of isolated petechiae in association with the vaccines administered to young infants in the current Dutch childhood immunisation program in the last 4 years.
DLS is not mentioned in the SmPC of Infanrix hexa®, Prevenar® nor in the SmPC of Synflorix®. Over the last 4 years, the Netherlands Pharmacoviligence Centre has received 125 reports with DLS as an AEFI.

Reports

The database of the Netherlands Pharmacovigilance Centre Lareb was screened for reports where one of the four vaccines (Infanrix hexa®, Synflorix,®, Pediacel® and Prevenar®) were given, associated with either petechiae or skin discolouration. This resulted in 49 cases of isolated petechiae and 149 cases of skin discoloration either with or without petechiae.

Table 1. number of reports of isolated petechiae, skin discolouration with petechiae and skin discolouration without petechiae per vaccination moment and per vaccine combination.

Vaccination moment	Vaccine combination	Isolated petechiae	Skin discolouration with petechiae	Skin discolouration without petechiae
1 (age 2 months)	Infanrix hexa® / Synflorix®	15	7	33
1 (age 2 months)	Pediacel® / Synflorix®	4		9
1 (age 2 months)	Pediacel® / Prevenar®		1	8

Vaccination moment	Vaccine combination	Isolated petechiae	Skin discolouration with petechiae	Skin discolouration without petechiae
1 (age 2 months)	Prevenar®		1	
2 (age 3 months)	Infanrix hexa® / Synflorix®	9	3	17
2 (age 3 months)	Pediacel® / Synflorix®	3	1	5
2 (age 3 months)	Pediacel® / Prevenar			9
2 (age 3 months)	Infanrix hexa® / Prevenar®		1	1
2 (age 3 months)	Infanrix hexa®	1		7
3 (age 4 months)	Infanrix hexa® / Synflorix®	9	6	21
3 (age 4 months)	Pediacel® / Synflorix®	3	1	4
3 (age 4 months)	Infanrix hexa® / Prevenar®	1	1	
3 (age 4 months)	Pediacel® / Prevenar®	2	1	2
3 (age 4 months	Synflorix®			1
4 (age 11 months)	Infanrix hexa® / Synflorix®	2		3
4 (age 11 months)	Pediacel® / Synflorix®	-		1
4 (age 11 months)	Pediacel® / Prevenar®	-		3
4 (age 11 months)	Infanrix hexa® / Prevenar®			1
Vaccination moment not reported	Infanrix hexa® (and MMR-Vaxpro® and Men C)			1
Totals		49	23	126

At the Netherlands Pharmacovigilance Centre the AEFI Discoloured Leg Syndrome is coded as “skin discolouration” since the term discoloured leg syndrome is not present in the used MedDRA code list. The MedDRA term “skin discolouration” is therefore not only preserved for the AEFI discoloured leg syndrome, but is used for a variety of symptoms concerning discolouration of the skin, including discolouration of skin in the face (Harlequin like reactions), at the injection site and in combination with hypotonic–hyporesponsive episode (HHE).
It was checked in how many cases of 149, the reported symptoms concerned DLS as defined in the literature [2, 7, 8]. This appeared to be 125 reported cases. For 13 cases it was not clear whether it concerned DLS or other symptoms and in 11 cases it did not concern DLS.
DLS is often reported accompanied by fierce crying and in a number of reports accompanied by petechiae. Table 1 shows that in 23 cases, skin discolouration was accompanied by petechiae. These 23 cases all concerned DLS according to the definition.

Table 2 (appendix) shows the details of the reported isolated petechiae.

As seen in table 1 and 2, the majority of the reported petechiae occurred below the age of 5 months. Only in 2 reported cases, the symptoms appeared after the 4th vaccination (approximately 11 months of age).
Petechiae were most of the time situated on the legs (35) but also on other parts of the body (13). In one case, the location is unknown. The latency varied from 3 minutes to 2 weeks, in the majority of the cases the petechiae were noticed within 2 days after vaccination. The duration of the petechiae varied from a few hours to 1,5 weeks. In the majority of the cases, the petechiae disappeared within 1 week after appearance.

Other sources of information

SmPC
Petechiae is not mentioned as AEFI in the SmPC of Pediacel®, Infanrix hexa®, Synflorix®, and Prevenar® [3-6]
Discoloured leg syndrome is only mentioned in the SmPC of Pediacel® in section 4.8 Undesirable effects, *c. Description of selected adverse reactions:*
"Edematous reactions affecting one or both lower limbs have occurred following vaccination with *H. influenzae* type b containing vaccines. When this reaction occurs, it does so mainly after primary injections and is observed within the first few hours following vaccination. Associated symptoms may include cyanosis, redness, transient purpura and severe crying. All events resolved spontaneously without sequelae within 24 hours" [3].

Literature
No literature involving petechiae and vaccination was found on Pubmed.
1 article was found concerning Discoloured leg syndrome and vaccination [2].
In this study, DLS was defined as an even or patchy red, blue or purple discoloration of the leg(s) and/or leg petechiae with or without swelling. Red, blue, purple discoloration and isolated petechiae were reported in 39, 19, 27 and 14% of the cases, respectively. Of the 1162 AEFI cases, 1105 were considered to be related to the vaccination, based on a predefined risk window with symptom onset after vaccination (48 h for discolorations and 2 weeks for petechiae). DLS was frequently accompanied by fierce crying (78%). The median time interval between vaccination and the occurrence of DLS was 3.8 +/- 46.7 h, and the median duration was short (2 +/- 61.7 h). Discoloured leg syndrome manifested mainly after the first and/or second vaccination. Advancing the vaccination schedule from 3 to 2 months of age caused a small increase in DLS. Therefore, the occurrence of DLS may be slightly age-dependent and self-limiting. The pathophysiology is unknown but may be the result of a vasomotor reaction.

DLS as AEFI after immunisation with inactivated vaccines is reported with an incidence of 1 to 2,000 vaccinated children [7-8].

Databases
The WHO database as well as the Eudravigilance database are not useful to check the reports on the given combinations of vaccines. The reasons for this is that it is not possible to search on combination of vaccines or to evaluate the injection moment since these differ between countries. Furthermore, other countries will not always use the same MedDRA term for DLS as Lareb. At last, it is also not possible to identify the cases in which the DLS was accompanied by petechiae.

Mechanism
The exact mechanism for either petechiae and DLS after vaccination is not clear. Possibly the symptoms are based on a vasomotor reaction [2]. It might be a misbalance of the regulation of the blood pressure in the small vessels of the skin at young age. In young infants, the regulation of the autonomic nerve system is still in development. This theory is being supported by the finding that advancing the vaccination schedule from 3 to 2 months of age caused a small increase in DLS. [4]
This would also explain the fact that in our cases, the symptoms mostly occur at a young age (i.e. after the first 3 vaccination moments). DLS manifested mainly after the first and/or second vaccination in the study of Kemmeren et al. [2]. Furthermore, the discoloration does not radiate form the injection site and therefore differs from local injection site reactions. If the above mechanism is correct, the reactions are not related to the vaccine, but are a reaction to the vaccination as a procedure.
Since the intensity and frequency of petechiae and DLS after vaccination do not increase with consecutive doses, these reactions not seem to be an immunologic reaction.

Discussion and Conclusion

In the period between 01 January 2011 and 18 May 2015, Lareb received 49 reports of reported petechiae concerning infants vaccinated with DPTP-Hib-(hepB) and pneumococcal vaccine (7-valent or 10-valent).
The children spontaneously recovered from the petechiae, mostly within 1 week.
Since petechiae can be an accompanying symptom of DLS, it is possible that the reported isolated petechiae have arisen after DLS without noticing the DLS itself, because in many cases the duration of DLS is short [2].

Even though petechiae can be an adverse event of the vaccination (AEFI), it should be noted that it cannot be trivialized since petechiae can also be a symptom of severe underlying conditions such as meningitis. In case of severe causes for petechiae, the child might also have other symptoms such as pyrexia and/or drowsiness, but this is not mandatory. There are also other possible coincidental conditions that can cause the petechiae, such as fierce crying (petechiae on the head) and a viral infection.
In addition a query using “Infanrix hexa and PT petechiae” and “Pediacel and PT petechiae” resulted in 75 reports. For the details see table 3 in the appendix.

In the period between 01 January 2011 and 18 May 2015, Lareb received 125 reports of reported DLS as defined in the literature, concerning infants vaccinated with DPTP-Hib-(hepB) and pneumococcal vaccine (7-valent or 10-valent).
After discussion with the Medicine Evaluation Board, it was agreed that at this moment it is too early to mention the syndrome DLS as such in the SmPC’s of the vaccines used in the current routine childhood immunisation programme. Therefore a list of Preferred Terms which describes the various symptoms of DLS is given in this document which need to be checked whether these are covered in the various SmPC’s (see table 4 appendix). Furthermore, we suggest a synchronisation of the SmPC’s of Pediacel® to the current used vaccines (Infanrix hexa® and Synflorix®) concerning the text which explains the possible occurrence of clustered symptoms of discoloured legs:
“Edematous reactions affecting one or both lower limbs have occurred following vaccination with *H. influenzae* type b containing vaccines. When this reaction occurs, it does so mainly after primary injections and is observed within the first few hours following vaccination. Associated symptoms may include cyanosis, redness, transient purpura and severe crying. All events resolved spontaneously without sequelae within 24 hours” [3].
The text should be adapted since it does not concerns exclusively HIB containing vaccines. Furthermore, in the routine childhood immunisation programme, 2 vaccines are administered simultaneously. It is therefore not to tell which vaccine contributes to the AEFI.
Even though the syndrome is not widely accepted as such, it is the opinion of Lareb that the cluster of symptoms (and thus the Discoloured Leg Syndrome) could be recognised by both parents and health care professionals. In case all symptoms are separately reported in the Eudravigilance database, the cluster symptoms will never be recognised as such.

Due to the finding of 49 reports of petechiae after vaccination at the age of 2, 3, 4 and 11 months, it should be considered to mention petechiae in section 4.4 of the SmPC of Infanrix hexa®, Synflorix,®, Pediacel® and Prevenar®. It should be explained that petechiae can occur at young infants, particularly after the first 3 vaccinations. These petechiae are located on the legs and lower abdomen and appear within 2 weeks after vaccination. It should also be explained that these petechiae can be part of discoloured leg syndrome. Finally, it should be indicated that petechiae can be a symptom of severe underlying conditions and should therefore never be denied.

Due to the finding of 125 reports of clustered symptoms after vaccination at the age of 2, 3, 4 and 11 months (described as DLS in the article of Kemmeren et al.), it should be considered to synchronise the SmPC’s of the current used vaccines in the Dutch routine childhood immunisaiton programme (Infanrix hexa® and Synflorix®) with the SmPC of Pediacel® in section 4.8 Undesirable effects, c. Description of selected adverse reactions.

- “Petechiae should be mentioned in section 4.4 of the SmPC of Pediacel®, Infanrix hexa®, Synflorix®, and Prevenar® ”
- The SmPC of Infanrix hex[a®] and Synflorix® Section 4.8 Undesirable effects, c. Description of selected adverse reactions should be synchronized with this section in the SmPC of Pediacel® and adapted to: “Edematous reactions affecting one or both lower limbs have occurred following vaccination. When this reaction occurs, it does so mainly after primary injections and is observed within the first few hours following vaccination. Associated symptoms may include cyanosis, redness, transient purpura and severe crying. All events resolved spontaneously without sequelae”

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Table 2: reported isolated petechiae at Lareb

Patient, Number, Sex, Vaccination moment, Source	Drug (single administration)	Concomitant medication	Suspected adverse drug reaction	Time to onset, Outcome
A, 121098, F, 3, Consumer	DPTP-Hib vaccine (Pediacel) pneumococcal vaccine 7 types (Prevenar)		screaming petechiae	2 hour, Recovered 8 hour Recovered
B, 122959, F, 1, Community health service	DPTP-Hib vaccine (Pediacel)	pneumococcal vaccine 10 types (Synflorix)	petechiae , injection site swelling	unknown hour, Recovered
C, 123148, M, 3, Community health service	DPTP-Hib-hepB vaccine (Infanrix hexa) pneumococcal vaccine 7 types (Prevenar)		viral infection petechiae	8 hour, Recovered 8 hour, Recovered
D, 123280, F, 1, Community health service	DPTP-Hib vaccine (Pediacel) pneumococcal vaccine 10 types (Synflorix)		petechiae	hour, Recovered
E, 125996, M, 3, Consumer	DPTP-Hib vaccine (Pediacel) pneumococcal vaccine 10 types (Synflorix)		petechiae body temperature increased	4 hour, Recovered 4 hour, Recovered
F, 126376 M, 3, Community health service	DPTP-Hib vaccine (Pediacel) pneumococcal vaccine 7 types (Prevenar)		petechiae	32 hour, Recovered
G, 127304, F, 2, Community health service	DPTP-Hib vaccine (Pediacel) pneumococcal vaccine 10 types (Synflorix)		petechiae	1 day, Recovered
H, 128523, F, 1, Community health service	DPTP-Hib-hepB vaccine (Infanrix hexa) pneumococcal vaccine 10 types (Synflorix)		petechiae	2 day, Recovering
I, 128648, F, 2, Community health service	DPTP-Hib vaccine (Pediacel) pneumococcal vaccine 10 types (Synflorix)		petechiae	unknown, Recovered
J, 128659, M, 3, Consumer	DPTP-Hib vaccine (Pediacel) pneumococcal vaccine 10 types (Synflorix)		petechiae malaise	2 days, Recovered unknown Recovered
K, 129116, M, 1, Community health service	DPTP-Hib-hepB vaccine (Infanrix hexa) pneumococcal vaccine 10 types (Synflorix)		petechiae	3 minute, Not recovered

Patient, Number, Sex, Vaccination moment, Source	Drug (single administration)	Concomitant medication	Suspected adverse drug reaction	Time to onset, Outcome
L, 129119, F, 1, Community health service	pneumococcal vaccine 10 types (Synflorix) DPTP-Hib vaccine (Pediacel)		petechiae	2 week, Recovered
M, 129148, F, 3, Community health service	pneumococcal vaccine 10 types (Synflorix)	DPTP-Hib vaccine (Pediacel)	petechiae	1 day, Recovered
N, 129992, F, 1, Community health service	DPTP-Hib vaccine (Pediacel) pneumococcal vaccine 10 types (Synflorix)		petechiae	1 week, Recovered
O, 130389, M, 2, Community health service	pneumococcal vaccine 10 types (Synflorix) DPTP-Hib vaccine (Pediacel)		pyrexia petechiae	1 hour, Recovered 10 day, Recovered
P, 130625, M, 2, Community health service	pneumococcal vaccine 10 types (Synflorix) DPTP-Hib-hepB vaccine (Infanrix hexa)		petechiae	10 minute, Recovered
Q, 136424, M, 3, Specialist doctor	DPTP-Hib-hepB vaccine (Infanrix hexa) pneumococcal vaccine 10 types (Synflorix)		petechiae	2 day, Unknown
R, 139393, F, 2, Consumer	DPTP-Hib-hepB vaccine (Infanrix hexa) pneumococcal vaccine 10 types (Synflorix)		petechiae influenza like illness	unknown day, Recovered unknown hour, Recovered
S, 144289, F, 1, Consumer	DPTP-Hib-hepB vaccine (Infanrix hexa) pneumococcal vaccine 10 types (Synflorix)		petechiae	unknown hour, Recovering
T, 144577, M, 2, Community health service	DPTP-Hib-hepB vaccine (Infanrix hexa) pneumococcal vaccine 10 types (Synflorix)		petechiae	4 hour, Recovered
U, 146605, F, 2, Consumer	DPTP-Hib-hepB vaccine (Infanrix hexa) pneumococcal vaccine 10 types (Synflorix)		pyrexia crying petechiae	5 hour, Recovered 5 hour, Recovered 5 hour, Recovered
V, 151240, F, 1, Community health service	DPTP-Hib-hepB vaccine (Infanrix hexa) pneumococcal vaccine 10 types (Synflorix)		petechiae	5 minute, Recovered

Patient, Number, Sex, Vaccination moment, Source	Drug (single administration)	Concomitant medication	Suspected adverse drug reaction	Time to onset, Outcome
W, 153344, F, 2, Consumer	DPTP-Hib-hepB vaccine (Infanrix hexa) pneumococcal vaccine 10 types (Synflorix)		injection site inflammation petechiae pyrexia body temperature decreased miliaria vomiting pallor	5 hour, Recovered 5 hour, Recovered 7 hour, Recovered 5 hour, Recovered 6 hour, Recovered 5 hour, Recovered 5 hour, Recovered
X, 156873, F, 1, Consumer	DPTP-Hib-hepB vaccine (Infanrix hexa) pneumococcal vaccine 10 types (Synflorix)		petechiae respiratory syncytial virus infection	4 day, Recovered 4 day, Recovered
Y, 156874, F, 2, Consumer	DPTP-Hib-hepB vaccine (Infanrix hexa) pneumococcal vaccine 10 types (Synflorix)		petechiae	1 day, Recovering
Z, 157001, M, 2, Consumer	DPTP-Hib-hepB vaccine (Infanrix hexa) pneumococcal vaccine 10 types (Synflorix)		petechiae	106 hour, Recovering
AA, 157008, F, 3, Community health service	DPTP-Hib-hepB vaccine (Infanrix hexa) pneumococcal vaccine 10 types (Synflorix)		petechiae	1 day, Not recovered
AB, 157465, F, 2, Consumer	pneumococcal vaccine 10 types (Synflorix) DPTP-Hib-hepB vaccine (Infanrix hexa)		petechiae	4 day, Recovering
AC, 157836, M, 1, Consumer	DPTP-Hib-hepB vaccine (Infanrix hexa) pneumococcal vaccine 10 types (Synflorix)		petechiae	36 hour, Recovering
AD, 157843, F, 2, Community health service	DPTP-Hib-hepB vaccine (Infanrix hexa) pneumococcal vaccine 10 types (Synflorix)		petechiae	28 hour, Recovered
AE, 158066, M, 3, Specialist doctor	DPTP-Hib-hepB vaccine (Infanrix hexa) pneumococcal vaccine 10 types (Synflorix)		purpura petechiae	6 hour, Recovering 6 hour, Recovered

Patient, Number, Sex, Vaccination moment, Source	Drug (single administration)	Concomitant medication	Suspected adverse drug reaction	Time to onset, Outcome
AF, 158302, M, 3, Community health service	DPTP-Hib-hepB vaccine (Infanrix hexa) pneumococcal vaccine 10 types (Synflorix)		petechiae	1 day, Recovered
AG, 158587, M, 1, Community health service	DPTP-Hib-hepB vaccine (Infanrix hexa) pneumococcal vaccine 10 types (Synflorix)		petechiae pyrexia	1 day, Recovered 12 hour, Recovered
AH, 159999, F, 1, Community health service	DPTP-Hib-hepB vaccine (Infanrix hexa) pneumococcal vaccine 10 types (Synflorix)		petechiae	1 day, Recovered
AI, 163094, F, 1, Consumer	DPTP-Hib-hepB vaccine (Infanrix hexa) pneumococcal vaccine 10 types (Synflorix)		petechiae	5 hour, Recovered
AJ, 170133, F, 4, Consumer	DPTP-Hib-hepB vaccine (Infanrix hexa) pneumococcal vaccine 10 types (Synflorix)		petechiae	3 day, Recovered
AK, 174657, F, 1, Community health service	DPTP-Hib-hepB vaccine (Infanrix hexa) pneumococcal vaccine 10 types (Synflorix)	esomeprazol lactulose	petechiae crying injection site pain	3 minute, Recovering 4 hour, Recovered 4 hour, Recovered
AL, 179383, M, 1, Consumer	DPTP-Hib-hepB vaccine (Infanrix hexa) pneumococcal vaccine 10 types (Synflorix)		petechiae	2 day, Recovered
AM, 179496, F, 4, Consumer	pneumococcal vaccine 10 types (Synflorix) DPTP-Hib-hepB vaccine (Infanrix hexa)		injection site inflammation petechiae	1 day, Recovered 1 day, Recovered
AN, 179607, F, 3, Consumer	pneumococcal vaccine 10 types (Synflorix) DPTP-Hib-hepB vaccine (Infanrix hexa)		petechiae	4 Day, Not recovered
AO, 181046, M, 1, Consumer	DPTP-Hib-hepB vaccine (Infanrix hexa) pneumococcal vaccine 10 types (Synflorix)		petechiae pyrexia	1 day, Recovered 8 hours, Recovered

Patient, Number, Sex, Vaccination moment, Source	Drug (single administration)	Concomitant medication	Suspected adverse drug reaction	Time to onset, Outcome
AP, 181719, M, 1, Consumer	pneumococcal vaccine 10 types (Synflorix) DPTP-Hib-hepB vaccine (Infanrix hexa)		petechiae crying injection site swelling	6 day, Recovering 1 hour, Recovering 6 day, Recovering
AQ, 183559, F, 3, Consumer	DPTP-Hib-hepB vaccine (Infanrix hexa) pneumococcal vaccine 10 types (Synflorix)		petechiae	unknown hour, Unknown
AR, 187376, M, 2, Consumer	DPTP-Hib-hepB vaccine (Infanrix hexa)		petechiae	3 day, Recovered
AS, 188216, M, 3, Consumer	DPTP-Hib-hepB vaccine (Infanrix hexa) pneumococcal vaccine 10 types (Synflorix)		injection site inflammation petechiae pyrexia crying	5 hour, Recovering 5 hour, Recovered 5 hour, Recovering seconds, Recovering
AT, 189330, F, 3, Community health service	DPTP-Hib-hepB vaccine (Infanrix hexa) pneumococcal vaccine 10 types (Synflorix)		petechiae	3 hour, Recovered
AU, 193472, M, 1, Community health service	pneumococcal vaccine 10 types (Synflorix) DPTP-Hib-hepB vaccine (Infanrix hexa)		petechiae	10 minute, Recovered
AV, 194297, F, 3, Consumer	pneumococcal vaccine 10 types (Synflorix) DPTP-Hib-hepB vaccine (Infanrix hexa)		petechiae	6 day, Recovered
AW, 196850, M, 1, Community health service	DPTP-Hib-hepB vaccine (Infanrix hexa) pneumococcal vaccine 10 types (Synflorix)		petechiae	1 day, Recovered

Table 3: Query “Pediacel – MedDRA PT petechiae (cut-ff 29 Sep 2015) summary of causality assessment.

Lareb Database query Pediacel : petechiae (cut-off 29 Sep 2015)

serious									
definite	**probable**	**possible**	**unlikely**	**not assessable**	**latency**	**Pediacel**	**Prevenar**	**Synflorix**	**comment**
				RIVM 200600568	4 days	1			petechiae and apnoea, hospitalised, hypertrophic cardiomyopathy with arrhythmia diagnosed
	NL-RIVM-2007-00.247				x hrs	1	1		1 night hospitalisation for observation. No abnormalities during hospitalisation, lab results normal
				RIVM-2007-00.720	1,5 day	1	1		1 night hospitalisation for observation. Petechiae recovered after 2 days. No further information
				RIVM-2006-01.071	2 days	1	1		2 days after vaccination red skin discolouration both legs from groin to ankles. Few minutes later petechiae on the legs, expanding to abdomen. 1 night hospitalisation. No thrombocytopenia
	NL-RIVM-2009-01.942				3,5 hrs	1	1		causality concerns skin discolouration. Leg in which Pediacel was given was completely red and petechiae seen. Not swollen. Hospitalised for observation during which no abnormalities
			NL-RIVM-2009-01.649		18 hrs	1			causality concerns pneumonia. Hospitalisation due to suspicion of meningitis; Appeared to be pneumonia and dehydration.
	NL-RIVM-2010-00.842				8 hrs	1	1		Body temperature 38,4. Meningitis suspected. LP performed. IV antibiotics. Cultures were clean/negative, also viral culture. Conclusion hospital: fever and petechiae, most likely caused by viral infection. RIVM causality regarding petechiae and fever: probable.
			NL-RIVM-2010-01.040		14,6 wks	1			Third DKTP without Hib administered. Fever: antibiotics. Then developed haematomas. After a month antibiotics because of gastroenteritis. Next day petechiae and hospitalized. Thrombocytes count zero. Suspicion starting meningitis: cefotaxim given. No abnormalities in blood seen. Working diagnosis ITP was made. Antibiotics stopped, discharged. No increase thrombocytes. Prednisone treatment was started. Thereafter recovered fast. RIVM causality regarding ITP was unlikely.
	NL-RIVM-2008-00.661				1,5 day	1	1		Admitted to the hospital on the day of vaccination due to HHE, discharged and re-admitted when the petechiae on lower legs and few on arms and in

									neck. 1 night hospitalisation for observation.
		NL-RIVM-2010-00.945			9 day	1	1		Petechiae and haematoma. Conclusion at hospital: Almost 1 year old girl with isolated thrombocytopenia, developed at the age of 11,5 month. Most probable diagnosis: Acute ITP
0	**4**	**1**	**2**	**3**		**10**	**7**	**0**	

non-serious									
definite	**probable**	**possible**	**unlikely**	**not assessable**	**latency**	**Pediacel**	**Prevenar**	**Synflorix**	**comment**
			NL-LRB-64635		1,5 hrs	1	1		petechiae on trunk and arms
		NL-RIVM-2007-00.002			1 week	1			on one lower leg
		NL-RIVM-2008-00.140			2 hrs	1	1		on head and neck
	NL-RIVM-2008-00.392				0,9 day	1	1		Right upper leg
	NL-RIVM-2008-00.430				3 days	1	1		on both lower legs and feet
	NL-RIVM-2008-00.511				2 wks	1	1		RIVM causality assessment regarding skin discolouration (discoloured legs)
	NL-RIVM-2008-00.614				1 day	1	1		one dozen on each leg
		NL-RIVM-2008-00.647			1 day	1	1		dozens on lower legs following directly after discoloured legs. RIVM causality assessment regarding skin discolouration (discoloured legs)
			NL-RIVM-2008-00.648		1 week	1	1		on lower legs following directly after discoloured legs. RIVM causality assessment regarding skin discolouration (discoloured legs)
			NL-RIVM-2008-00.649		5 wks	1	1		on lower legs following directly after discoloured legs. Re-occurred 10 weeks after vaccination. RIVM causality assessment regarding skin discolouration (discoloured legs)
	NL-RIVM-2008-00.711				3,5 hrs	1	1		on both legs, following skin discolouration of the right leg (groin to foot).
		NL-RIVM-2008-00.719			2 days	1	1		on right lower leg and right foot
	NL-RIVM-2008-00.732				2 hrs	1	1		on left lower leg
		NL-RIVM-2008-00.876			3,5 days	1	1		on both lower legs
	NL-RIVM-2008-00.881				8 hrs	1	1		on left upper and lower leg

NL-RIVM-2008-00.902					2 days	1	1		RIVM causality assessment regarding injection site inflammation. Around the injection site inflammation, red spots present spread over het complete upper leg
	NL-RIVM-2008-00.936				6 hrs	1	1		on lower legs following directly after discoloured legs. RIVM causality assessment regarding skin discolouration (discoloured legs)
	NL-RIVM-2008-01.136				6 hrs	1	1		on both lower legs
	NL-RIVM-2009-00.169				0,9 days	1	1		around the injection site, following discoloured right upper leg. RIVM causality assessment regarding skin discolouration (discoloured legs)
	NL-RIVM-2009-00.745				15 mins	1	1		dozens on both lower legs
			NL-RIVM-2009-00.422		6 days	1	1		crying, slight fever, sleepiness and cough with a latency of 3 days, appetite decreased nos with a latency of 4 days, lymphadenopathy with a latency of 5 days and exanthema and petechiae with a latency of 6 days. Antibiotics were prescribed. Henoch Schonlein?
	NL-RIVM-2009-01.636				1 day	1	1		on left lower leg
	NL-RIVM-2009-01.706				8 hrs	1	1		both legs spread from groin to toes, following discoloured legs from toe to diaper.
		NL-RIVM-2009-01.726			5 mins	1	1		Several petechiae on both upper arms.
	NL-RIVM-2009-01.745				6 hrs	1	1		on legs following directly after discoloured legs. RIVM causality assessment regarding skin discolouration (discoloured legs)
			NL-RIVM-2009-01.746		6 wks	1	1		First discoloured legs (both legs from groin to feet). Next morning a lot of petechiae on front side of the upper legs, on calves and popliteal fossa's RIVM causality assessment regarding skin discolouration (discoloured legs)
	NL-RIVM-2009-01.787				8 hrs	1	1		On both legs directly following skin discolouration of both legs (from toe to groin). RIVM causality assessment regarding skin discolouration (discoloured legs)
	NL-RIVM-2009-01.821				5,5 hrs	1	1		HHE, also 1 spot on left right lower was seen
		NL-RIVM-2009-01.948			1 day	1	1		About 70 petechiae on left cheek and ear.
	NL-RIVM-2009-01.982				0,9 day	1	1		Day after vaccination petechiae on both legs. One leg more than the other. Also swelling of one leg.
		NL-RIVM-2009-02.139			1 day	1	1		around both knees
	NL-RIVM-2009-02.154				4 hrs	1	1		Together with skin discoloration legs seen (red, from groin to ankles). RIVM causality assessment

									regarding skin discolouration (discoloured legs)
			NL-RIVM-2009-02.294		3 days	1	1		On legs following skin discolouration of one leg. RIVM causality assessment regarding skin discolouration (discoloured legs)
	NL-RIVM-2009-02.541				13 hrs	1	1		RIVM causality assessment regarding skin discolouration.
	NL-RIVM-2010-00.112				4 hrs	1	1		3 petechiae on legs following skin discolouration (both legs and feet red with blue stains, scrotum and part of abdomen blue). RIVM causality assessment regarding skin discolouration (discoloured legs)
	NL-RIVM-2010-00.196				12 hrs	1	1		both lower legs up to just above the knees a lot of petechiae
	NL-RIVM-2010-00.713				0,9 days	1	1		in the evening left leg, morning after also right leg
	NL-RIVM_2010-00.584				1,5 days	1	1		on both legs
	NL-RIVM-2010-00.930				1,5 days	1	1		on both legs
	NL-RIVM-2010-00.931				1,5 days	1	1		on both legs
			NL-RIVM-2010-00.884		2 wks	1	1		left lower leg 10-20 purpura. Lasted one week. Reoccurrence one month after purpura, petechiae seen on bottom, sole of feet and both lower legs. Conclusion outpatient clinic: viral infection, Von Willebrand disease or Henoch Schonlein?
		NL-RIVM-2009-01.446			4 days	1	1		on both legs, primarily on lower legs
	NL-RIVM-2010-00.950				5 hrs	1	1		On leg, following skin discolouration (left leg). RIVM causality assessment regarding skin discolouration (discoloured legs)
	NL-RIVM-2010-00.951				5 hrs	1	1		both legs following skin discolouration (from diaper to feet). RIVM causality assessment regarding skin discolouration (discoloured legs)
	NL-RIVM-2010-01.146				4,5 hrs	1	1		breath holding spell (5 times within 1 hour), during crying petechiae seen on lower legs, right more than left and few on upper legs.
	NL-RIVM-2010-01.185				0,9 days	1	1		morning following the day of vaccination petechiae all over both legs
	NL-RIVM-2010-01.210				1,5 days	1	1		right lower leg
	NL-RIVM-2010-01.464				x days	1	1		RIVM causality assessment regarding LLT skin hyperemia
		NL-LRB-121098			8 hrs	1	1		between 1st and 2nd vaccination also petechiae: viral according to paediatrician. 2 hours after vaccination persistent screaming, when calmed, 8 hours after vaccination petechiae on legs

		NL-LRB-122959			x hrs	1		1	petechial rash on left leg
		NL-LRB-123280			x hrs	1		1	petechiae in neck, right side, in an area of 10x10 cm
		NL-LRB-125996			4 hrs	1		1	crying vehemently during 10-15 minutes while vaccination was given. 4 hours after vaccination 30 petechiae on head and under hair and behind ears
	NL-LRB-126376				32 hrs	1	1		on both legs: one side whole leg approximately 100 petechiae, other leg only on shin and calve
		NL-LRB-127304			1 day	1		1	both lower legs (about 10 left leg , 3 to 4 right leg)
	NL-LRB128648				2 days	1		1	on left leg (Pediacel). Positive rechallenge (but synflorix side)
	NL-LRB128659				2 days	1		1	both legs, positive rechallenge
		NL-LRB-129119			2 wks	1		1	both feet, right more than left, diffuse spread
	NL-LRB-129148				1 day	1		1	left leg (synflorix) from foot to knee mostly front side.
	NL-LRB-129992				1 wks	1		1	both lower legs
		NL-LRB-130389			10 days	1		1	on both legs, paediatrician concluded findings suiting Henoch Schonlein or possibly caused by vaccination
1	**36**	**16**	**7**	**0**		**60**	**49**	**10**	

Lareb Database query Infanrix Hexa : petechiae (cut-off 3 Aug 2015)

serious									
Definte	**probable**	**possible**	**unlikely**	**Not assessable**	**latency**	**Infanrix Hexa**	**Prevenar**	**Synflorix**	**comment**
			NL-LRB-123148		8 hrs	1	1		parechovirus infection more likely cause (40C fever)
			NL-LRB-139393		days	1		1	flu-like symptoms: possible, however unusual long persistence (days) and a viral cause deemed more likely by clinician
	NL-LRB-156873				4 days	1		1	Hospitalisation was because of coincidental Respiratory syncytial virus infection, not due to petechiae. Causality for the petechiae due to vaccination against DPTPHib HepB and pneumococci was considered probable because the same symptoms occurred after the 2nd and 3rd vaccinations as well.
	NL-LRB-158066				6 hrs	1		1	Only petechia after 3rd dose (at 4 months of age). No AEs after first two doses.
		NL-LRB-158587			1 day	1		1	Petechia on feet and the lower leg at both sites.

									Hospitalisation due to petechia and increased CRP. Positive rechallenge after second dose. In both instances pyrexia was also present
0	**2**	**1**	**2**			**5**	**1**	**4**	
non-serious									
Definite	**probable**	**possible**	**unlikely**		**latency**	**Infanrix Hexa**	**Prevenar**	**Synflorix**	**comment**
		NL-RIVM-2010-00.648			10-15 min	1	1		petechiae on face due to severe crying
		NL-RIVM-2010-00.826			10-15 min	1	1		petechiae on face due to severe crying
		NL-RIVM-2010-01.055			2.5 hrs	1	1		
		NL-RIVM-2009-02.136			x hrs	1	1		developed ITP
	NL-LRB-128523				2 days	1		1	
			NL-LRB-129116		3 min	1		1	petechiae confined to the hand
			NL-LRB-130625		10 min	1		1	limited number of spots (n=3), Medical history: deep neonatal Anaemia (Hb2.0). Palivizumab therapy was associated with petechiae with normal platelet count.
	NL-LRB-136424				2 days	1		1	purpura and petechiae on both legs. Especially on his lowerleg, some at the front side of his upperlegs, with a diameter up to 0,5cm.
	NL-LRB-144289				x hrs	1		1	red spots on whole legs with a diameter of 2-4 mm. In the course of 15 minutes the spots turned into black and remained for a couple of hours
		NL-LRB-144577			4 hrs	1		1	8 Hours after the vaccinations 3-4 petechiae appeared on his head and about 50 on his body. Nothing peculiar was seen on his extremities.
	NL-LRB-146605				5 hrs	1		1	positive rechallenge
	NL-LRB-151240				5 min	1		1	present in the neck
		NL-LRB-153344			5 hrs	1		1	negative rechallenge, pyrexia (problable) injection site inflammation (definte)
	NL-LRB-156874				1 day	1		1	purple blue spots with a diameter of less than 1 mm were visible at left lower leg.
		NL-LRB-157001			106 hrs	1		1	ten spots were detected with a size of 1-4 mm at

									the inside of the knee
		NL-LRB-157008			1 day	1		1	at the right lower leg (Synflorix side) 14 petechiae were seen, at the left leg (Infanrix hexa side) about 3-4
		NL-LRB-157465			4 days	1		1	spots on both legs
		NL-LRB-157836			36 hrs	1		1	legs and feet
	NL-LRB-157843				28 hrs	1		1	on right leg
		NL-LRB-158302			1 day	1		1	petechiae on his trunk and arms
	NL-LRB-159999				1 day	1		1	petechiae on right lower leg (Synflorix side)
	NL-LRB-163094				5 hrs	1		1	red/purple points and spots were seen on the right lower leg and foot.
		NL-LRB-170133			3 days	1		1	positive rechallenge, On most occasions the petechiae were localised at hands and wrist, and only once at a lower leg.
	NL-LRB-174657				3 mins	1		1	petechial rash (neck and face), crying and injection site pain
	NL-LRB-179383				2 days	1		1	7 purple spots in total on both legs
	NL-LRB-179496				1 day	1		1	confounded by injection site inflammation (probable) at left leg became red, warm and painful, size 3 cm by 3 cm. The mother noticed spread over the whole left leg small red spots
		NL-LRB-179607			4 days	1		1	20 blue dots on both legs
	NL-LRB-181046				1 day	1		1	30 blue spots to be seen on left lower leg and foot
	NL-LRB-181061				less than 1 day	1		1	lower leg
		NL-LRB-181719			6 days	1		1	with injection site swelling, petechia and crying
		NL-LRB-183559			hrs	1		1	
		NL-LRB-187376			3 days	1		1	positive rechallenge
		NL-LRB-188216			5 hrs	1		1	with injection site inflammation, petechial rash, pyrexia and persistent crying
	NL-LRB-189330				3 hrs	1		1	several small blue spots on right lower leg
		NL-LRB-193472			10 min	1		1	following severe crying many petechiae on face and neck
		NL-LRB-194297			6 days	1		1	hundreds of little blue hairvessels in the right leg
	NL-LRB-196850				1 day	1		1	10-15 purple spots with a diameter of 0,5 cm at his forehead and at the border of the hair
0	16	19	2			37	4	33	

Table 4: List of Preferred Terms describing the various symptoms of DLS

- Skin discolouration (of (part of) the leg)
- Swelling of legs, Swelling femoral, swelling of feet, swelling of limb
- Petechiae
- Crying

The skin discoloration of the leg can involve the entire leg, one leg, only the upper leg, only the lower leg or the feet. The discoloration can involve the leg in which was vaccinated, or the opposite leg or even both legs. The discoloration can be red, blue or purple.