Overview 1 of reported AEFIs Vaxelis® compared to Infanrix hexa® at infant age

Introduction

At the end of 2018 in National Vaccination Program of the Netherlands (RVP) Infanrix hexa® was substituted by Vaxelis®. Vaxelis® has been licensed since February 15, 2016 [1]. It is a black triangle vaccine. Such products are subject of additional monitoring, so that new safety information can be established quickly. Pharmacovigilance Center Lareb will closely monitor Vaxelis® in the coming period on the basis of these spontaneous reports.

Until 2018, Infanrix hexa® was the diphtheria-pertussis-tetanus-IPV-HiB-hepB vaccine of choice in the RVP. Infanrix hexa® has been administered since 2011 at the age of 2, 3 and 4 months (primary series) followed by a first booster vaccination at the age of 11 months [2]. Children born before December 1, 2018, who started the primary series with Infanrix hexa®, will complete the primary series and first booster vaccination with Infanrix hexa®. For children born on December 1, 2018 or later, the primary series and first booster vaccination will be Vaxelis® [3].
At the age of 2, 4 and 11 months, the administration of DTP-IPV-HiB-HepB vaccine is usually combined with administration of a pneumococcal vaccination (Synflorix®) in the contralateral leg (table1).

Table 1. Vaccination scheme in the Netherlands at infant age.

Vaccination number	Age	Until December 1, 2018	After December 1, 2018
1	8 weeks	Infanrix hexa® + Synflorix®	Vaxelis® + Synflorix®
2	12 weeks	Infanrix hexa®	Vaxelis®
3	16 weeks	Infanrix hexa® + Synflorix®	Vaxelis® + Synflorix®
4	11 months	Infanrix hexa® + Synflorix®	Vaxelis® + Synflorix®

A monitoring will be carried out on the basis of the following questions:
1. Are there more adverse event following immunization (AEFI) reported after administration of Vaxelis® with or without Synflorix® than after administration of Infanrix hexa® with or without Synflorix®?
2. Are there more serious AEFIs reported after administration of Vaxelis® (/ Synflorix®) than after administration of Infanrix hexa® (/ Synflorix®)?
3. Are the AEFIs reported after administration of Vaxelis® (/ Synflorix®) comparable in number and type with Infanrix hexa (Synflorix®)?
4. Are there any findings after administration of Vaxelis® that require interventions?

To perform this monitoring, spontaneous reports of the age cohort of children born between 1-12-2018 and 1-12-2019 (Vaxelis cohort) will be compared with spontaneous reports of the age cohort of children born between 1-12-2017 and 1-12- 2018 (Infanrix hexa cohort).
A total of 4 overviews will be made. Figure 1 provides an overview of the comparable periods over time.

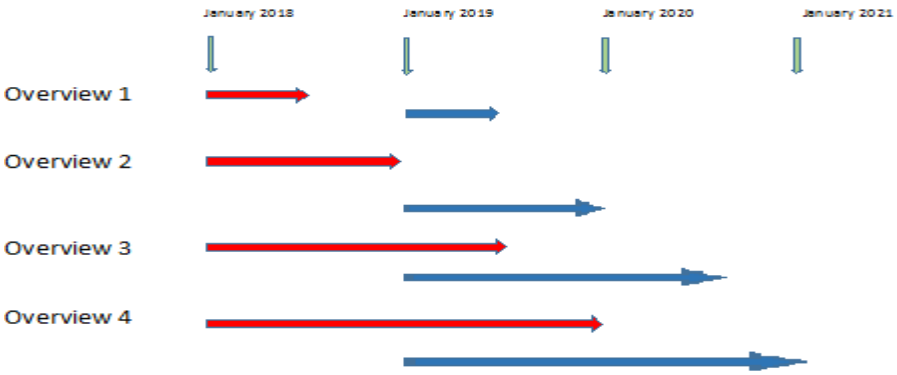

Figure 1 Comparable reporting periods in time for the overviews. Red arrows represent the Infanrix hexa cohort and the blue arrows the Vaxelis cohort.

- The first overview relates to reports from the Vaxelis cohort reported in the period January 1, 2019 to July 1, 2019 compared to reports from Infanrix hexa cohort reported in the period January 1, 2018 to July 1, 2018.
- Overview 2 relates to the period 1 January 2019 to January 1, 2020 (Vaxelis cohort) compared to the Infanrix hexa cohort for the period January 1, 2018 to January 1, 2019.
- Overview 3 relates to the period January 1, 2019 to July 1, 2020 (Vaxelis cohort) compared to the Infanrix hexa cohort for the period from 1 January 2018 to 1 July 2019.
- Overview 4 relates to the period 1 January 2019 to 1 January 2021 (Vaxelis cohort) compared to the Infanrix hexa cohort for the period 1 January 2018 to 1 January 2020.

In overview 4, the number of reports reported per vaccination moment of the Vaxelis cohort and the Infanrix hexa cohort will also be compared with the number of vaccinations per vaccination moment per vaccine. Reporting rates and rate ratios will be calculated based on this information. The reported AEFIs of Vaxelis will also be compared with the safety profile presented in section 4.8 of the Vaxelis SmPC. See Attachment 1.

Reports

In the Lareb database, spontaneous reports were selected after administration of Vaxelis® from children born between December 1, 2018 and June 1, 2019, which were received in the period from January, 1 2019 to July 1, 2019 (Vaxelis® cohort). Furthermore, the spontaneous reports were selected after the administration of Infanrix-hexa® from children born between December 1, 2017 and June 1, 2018, which were received in the period from January, 1 2018 to July 1, 2018 (Infanrix-hexa® cohort). Information about the brand name of the administered vaccine, batch number, vaccination date, vaccination number of the series, date of birth, age, gender and the reported AEFIs were collected from these reports.

Table 2. Overview of the number of number of spontaneous reports and reported AEFIs of Vaxelis® from children born between december 1, 2018 and June 1, 2019, which were received in the period from January, 1 2019 to July 1, 2019 (Vaxelis® cohort) and spontaneous reports and reported AEFIs of Infanrix hexa® from children born between December 1, 2017 and June 1, 2018, which were received in the period from January, 1 2018 to July 1, 2018 (Infanrix hexa® cohort).

Vaccination number series	Vaxelis® cohort		Infanrix hexa® cohort	
	Number reports	Number AEFIs	Number reports	Number AEFIs
1*	72 (63.7%)	238 (65.8%)	59 (65.6%)	157 (69.8%)
2*	23 (20.4%)	79 (21.8%)	19 (21.1%)	47 (20.9%)
3*	15 (13.3%)	36 (9.9%)	11 (12.2%)	19 (8.4%)
4*				
missing**	3 (2.7%)	9 (2.5%)	1 (1.1%)	2 (0.9%)
total	113 (100%)	362 (100%)	90 (100%)	225 (100%)

* only a limited number of children were old enough on June 30 to have reached the age for all 3 vaccination moments. None of the children were at that time old enough for vaccination number 4.

** If the vaccination number of the series is unknown, or deviates too much from the expected vaccination number based on age, the vaccination number is classified as missing

Table 2 provides an overview of the number of reports and the number of reported AEFIs from the Vaxelis cohort received between 1 January 2019 and 1 July 2019 and from Infanrix hexa cohort received between 1 January 2018 and 1 July 2018. The total number of reports reported as well the number of reports reported per vaccination number in the Vaxelis cohort is slightly higher than in the Infanrix hexa cohort over a comparable period a year earlier.

Serious reports and reported AEFIs

Table 3 provides an overview of the number of serious and non-serious reports per vaccination number of the series. According to the criteria formulated by Council for International Organizations of Medical Sciences criteria (CIOMS criteria), 8.8% of the Vaxelis® cohort are serious and 10% of the Infanrix hexa cohort. Both in the Vaxelis cohort and in the Infanrix hexa cohort, the most serious reports were received after the first administration (vaccination number 1) at approximately the age of 8 weeks (12.5% vs. 10.2%). At the first administration, Vaxelis® or Infanrix hexa® is often administered in combination with Synflorix® in the contralateral upper leg.

Table 3. Overview of the number of serious and non-serious spontaneous reports per vaccination number.

Vaccination number series	Vaxelis® cohort		Infanrix hexa® cohort	
	serious	Non-serous	serious	Non-serious
1*	9 (12.5%)	63 (87.5%)	6 (10.2%)	53 (89.8%)
2	1 (4.3%)	22 (95.7%)	2 (10.5%)	17 (89.5%)
3*		15 (100.0%)	1 (9.1%)	10 (90.9%)
4*				
9		3 100.0%)		1 (100.0%)
total	10 (8.8%)	103 (91.2%)	9 (10.0%)	81 (90.0%)

* During vaccination numbers 1, 2 and 3, both Vaxelis®and Infanrix hexa®are often co-administered with Synflorix® in the contralateral leg.

Serious AEFIs

Two deaths were reported in the Vaxelis cohort. In both cases it concerned a death after the first administration of Vaxelis® in combination with Synflorix® at the age of approximately 8 weeks. In both cases autopsy has been performed. One child died as a result of fulminant sepsis and the other child as a result of SIDS. On the basis of the information provided by the reporter, the result of the autopsy, and current knowledge in the literature, a relationship between the death and the administered vaccines was considered unlikely in either case. These conclusions were endorsed by the extern independent Clinical Advisory Board of Pharmacovigilance Center Lareb (KAR).
In the Infanrix hexa® cohort, no reports concerning the death of the patient were made in the comparable period a year before.

The other eight serious reports from the Vaxelis cohort concern reports of hospital admissions, seven times after vaccination number 1 and one time after the 2nd administration of only Vaxelis (vaccination number 2).
Four of these admissions are admissions in connection with short-lasting events that occur a few hours (4-8 hours) after vaccination. In these cases the following symptoms are often reported: pallor, hypotonia, and hyporesponsivity. These events are known in the literature as Hypotonic Hyporesponsive Event (HHE). Children with an HHE are often admitted to the hospital for 24-hour monitoring. Further investigations and monitoring usually show no abnormalities.
One report of hospitalization concerns a recurring short-lasting event (5-10 minutes) of a collapse-like event of crying, turning away of the eyes, breathing holding and pallor. The symptoms were eventually diagnosed by the reporting pediatrician as breath holding spells.
Three reports concern a hospital admission on suspicion of a convulsion. One of these reports concerns an event of dyspnea, fever and shaking a few hours after the first vaccination. Blood, urine tests and EEG showed no abnormalities. One report concerns a hospital admission of recurrent convulsion, followed by crying. The child recovered within 2 to 3 hours after hospitalization and after the administration of a paracetamol. There was also one report of a hospital admission of a convulsion (apnea, foam at the mouth and hypertonia) 6 days after the first vaccination. A brain scan showed no abnormalities.

Hospitalization was reported 9 times in the Infanrix hexa cohort. Four times it concerned an HHE, for which the child was admitted to the hospital for observation. This was three times after administration of the first vaccinations and once after the third vaccinations. One child was admitted to the hospital for apnea, possibly HHE after administration of the second Infanrix hexa®. The child also had a collapse after the first administration. One child was admitted to the hospital in connection with the drainage of an abscess after the first administration (positive culture: streptococcal group A). One child was briefly admitted to the hospital for observation in connection with pyrexia (40 Degrees Celsius) after the first vaccinations. Blood and urine tests showed no evidence of infection. One child was admitted for fever, rash, and peripheral swelling occurring 10 hours after the first vaccinations. The child was treated with an antihistamine and recovered. Once, a child was admitted due to persistent gastroesophageal reflux developed 4 to 5 days after the first vaccinations.

Non-serious AEFIs
Appendix two provides an overview of all reported non-serious AEFIs (coded MedDRA® Preferred Term (PT)) per System Organ Class (SOC) per cohort. Vaxelis cohort concerns 362 non-serious AEFIs reported in the period January 1, 2019 until July 1, 2019. Infanrix hexa cohort concerns 225 non-serious AEFIs reported in the comparable period one year before (January 1, 2018 until July 1, 2018). The number of reports and the number of AEFIs differs per vaccination number of the series at infant age. The vast majority of reports and reported AEFIs are reported after administration of the first vaccination at the age of 2 months. The type of reported AEFIs also differ per vaccination number of the series. For this reason, AEFIs are broken down by vaccination number. Appendix 3 to 6 provides an overview of the reported AEFIs per vaccination moment. After all vaccination numbers, more AEFIs are reported after administration of Vaxelis® (/ Synflorix®) than after administration of Infanrix hexa® (/ Synflorix®).

vaccination number 1
After the 1st administration 235 non-serious AEFIs have been reported in the Vaxelis® cohort against 157 AEFIs in the Infanrix hexa® cohort (Appendix 3). In particular, injection site reactions, such as injection site swelling, injection site redness, injection site pain and injection site inflammation, were slightly more frequently reported after administration of Vaxelis® / Synflorix® compared to Infanrix hexa® / Synflorix®. It seems that also fever, persistent crying and skin discolouration were slightly more frequently reported after administration Vaxelis® / Synflorix®.

vaccination number 2
After the 2nd administration 79 non-serious AEFIs have been reported in the Vaxelis® cohort against 47 AEFIs in the Infanrix hexa® cohort (Appendix 4). In particular, injection site reactions, such as injection site swelling, injection site redness, injection site pain and injection site inflammation, were slightly more frequently reported after administration of Vaxelis® compared to Infanrix hexa®. It seems that also persistent crying were slightly more frequently reported after administration of Vaxelis®.

vaccination number 3
After the 3rd administration 36 non-serious AEFIs have been reported in the Vaxelis® cohort against 19 AEFIs in the Infanrix hexa® (Appendix 5). It seems that HHE or symoms that meet the definition of HHE were more frequently reported after 3rd administration of Vaxelis®/ Synflorix® than after 3rd administration of Infanrix hexa®/ Synflorix®. It seems that also persistent crying were more frequently reported after administration of Vaxelis® / Synflorix®.

The reported AEFIs after vaccination numbers 2 and 3 in this overview should be viewed with caution, as the numbers and type of AEFIs are limited and only relate to a small group of children born between December 1 and February 28.

Other sources of information

SmPC
The SmPC from Vaxelis® was first published on 26-2-2016 and was last updated on 19-2-2019. Appendix 1 provides a copy of the list of AEFIs as shown in section 4.8 of the Vaxelis® SmPC. The list of AEFIs in table form shows less AEFIs compared to the table in 4.8 of the SmPC of Infanrix hexa® [4]. In particular, AEFIs such as HHE, collapse, convulsions, febrile convulsions, urticaria, angioedema and facial oedema are not listed in the table of 4.8, but as AEFIs that have been reported in post-marketing surveillance.

Discussion and conclusion
This report is the first overview of a total of four semi-annual reports in which the first birth cohort that will be vaccinated with Vaxelis® will be compared to the last birth cohort that will be vaccinated with Infanrix hexa®.

In the period January 1, 2019 - July 1, 2019 received Pharmacovigilance Centre Lareb 25% more spontaneous reports following administration of Vaxelis® (/ Synflorix®) than after administration of Infanrix hexa® (/ Synflorix®) in a comparable period one year before (January 1, 2018 July 1, 2018). In the Vaxelis cohort, 48% more AEFIs were reported compared to the Infanrix hexa cohort. The majority of these AEFIs are well-known, non-serious AEFIs.

The number of serious reports in the Vaxelis cohort is comparable to the number of serious reports in the Infanrix hexa cohort over the same period one year before. The type of serious AEFIs are also comparable between the two cohorts. About half of the hospitalizations in both cohorts concerns 24-hour monitoring after experiencing HHE or collaps. In the Vaxelis cohort three hospital admissions concern convulsion-like events, but in all 3 cases after further investigation the diagnosis convulsion could not be confirmed.
Possibly there is a slight increase in reactogenicity after administration of Vaxelis® compared to Infanrix hexa®. In the Vaxelis cohort, injection site reactions are slightly more frequently be reported after the first administration of Vaxelis® than after the first administration of Infanrix hexa®. It also seems that fever, persistent crying and skin discolouration are slightly more frequently reported. The next overviews will give more insight in this.

The first analysis of the reports of AEFI of Vaxelis® did not raise concern for safety or signals for new (aspects of) side effects.

References

1. https://www.ema.europa.eu/en/documents/product-information/vaxelis-epar-product-information_en.pdf
2. https://rijksvaccinatieprogramma.nl/over-het-programma
3. https://rijksvaccinatieprogramma.nl/20-addendum-overgang-van-infanrix-hexa-naar-vaxelis-dktp-hib-hepb
4. https://www.ema.europa.eu/en/documents/product-information/infanrix-hexa-epar-product-information_en.pdf

This signal has been raised on December 4, 2019. 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.

SmPC Vaxelis 4.8

Tabel 1: Lijst met bijwerkingen

Systeem/orgaanklasse	Frequentie	Bijwerkingen
Infecties en parasitaire aandoeningen	Soms	Rhinitis
Bloed- en lymfestelselaandoeningen	Soms	Lymfadenopathie
Voedings- en stofwisselingsstoornissen	Zeer vaak	Verminderde eetlust
	Soms	Verhoogde eetlust
Psychische stoornissen	Soms	Slaapstoornissen waaronder slapeloosheid, rusteloosheid
Zenuwstelselaandoeningen	Zeer vaak	Somnolentie
	Soms	Hypotonie
Bloedvataandoeningen	Soms	Bleekheid
Ademhalingsstelsel-, borstkas- en mediastinumaandoeningen	Soms	Hoesten
Maagdarmstelselaandoeningen	Zeer vaak	Braken
	Vaak	Diarree
	Soms	Buikpijn
Huid- en onderhuidaandoeningen	Soms	Huiduitslag, hyperhidrose
Algemene aandoeningen en toedieningsplaatsstoornissen	Zeer vaak	Huilen, prikkelbaarheid
		Erytheem op de injectieplaats, pijn op de injectieplaats, zwelling op de injectieplaats
		Pyrexie
	Vaak	Bloeduitstorting op de injectieplaats, induratie op de injectieplaats, nodules op de injectieplaats
	Soms	Huiduitslag op de injectieplaats, warmte op de injectieplaats, vermoeidheid

c- Beschrijving van de geselecteerde bijwerkingen

De volgende bijwerkingen zijn gemeld met andere vaccins die een of meer componenten of bestanddelen van Vaxelis bevatten, ongeacht oorzakelijkheid of frequentie.

Immuunsysteemaandoeningen
Overgevoeligheid (zoals huiduitslag, urticaria, dyspneu, erythema multiforme), anafylactische reactie (zoals urticaria, angio-oedeem, oedeem, gezichtsoedeem, shock).

Zenuwstelselaandoeningen
Convulsie, koortsconvulsie.

Algemene aandoeningen en toedieningsplaatsstoornissen
Bij kinderen is melding gemaakt van uitgebreide zwelling op het gevaccineerde ledemaat vanaf de injectieplaats tot voorbij een of beide gewrichten. Deze reacties beginnen binnen 24 tot 72 uur na de vaccinatie, kunnen gepaard gaan met erytheem, warmte, drukgevoeligheid of pijn op de injectieplaats en verdwijnen spontaan binnen drie tot vijf dagen. Het risico lijkt afhankelijk te zijn van het aantal eerdere doses acellulair pertussisbevattend vaccin, met een hoger risico na de vierde en vijfde dosis.

d- Premature zuigelingen

Apneu bij zeer vroeg geboren zuigelingen (≤ 28 weken zwangerschap) (zie rubriek 4.4.).

Appendix 2

Overview of reported non-serious AEFIs per SOC Vaxelis cohort (up to and including June 1019) and Infanrix hexa cohort (up to and including June 2018).

		Vaxelis cohort		Infanrix hexa cohort	
Systemic Organ Class (SOC)	**Pt**	**N**	**%**	**N**	**%**
infections and infestations	Ear infection	1	0,3		
	Nasopharyngitis			2	0,9
Blood and lymphatic system disorders					
Immune system disorders	Urticaria	1	0,3		
Metabolism and nutrition disorders	Decreased appetite	12	3,3	4	1,8
	Hypophagia	2	0,6		
	Increased appetite			1	0,4
	Thirst decreased			1	0,4
Psychiatric disorders	Anxiety	1	0,3		
	Apathy	1	0,3	1	0,4
	Breath holding	2	0,6	2	0,9
	Feeling jittery			2	0,9
	Insomnia	8	2,2	2	0,9
	Irritability	3	0,8	1	0,4
	Mood altered	1	0,3		
	Nervousness			1	0,4
	Restlessness	3	0,8		
	Sleep disorder	1	0,3		
	Slow response to stimuli	1	0,3	1	0,4
	Somnolence	10	2,8	14	6,2
Nervous system disorders	Apparent life threatening event			1	0,4
	Depressed level of consciousness	1	0,3	2	0,9
	Drooling	1	0,3		
	Exaggerated startle response	1	0,3		
	Febrile convulsion	1	0,3		
	Headache			1	0,4
	Hypertonia			2	0,9
	Hyporesponsive to stimuli	2	0,6	1	0,4
	Hypotonia	3	0,8	2	0,9
	Hypotonic-hyporesponsive episode	3	0,8	3	1,3
	Infantile back arching	1	0,3		
	Petit mal epilepsy	1	0,3		
	Syncope	2	0,6		
Vascular disorders	Livedo reticularis	1	0,3		
	Pallor	9	2,5	3	1,3
	Petechiae	1	0,3	2	0,9
	Vasodilatation			1	0,4
Cardiac disorders	Cardiac murmur			1	0,4
	Cyanosis			1	0,4
	Heart rate increased	1	0,3		
respiratory, thoracic and mediastinal disorder	Cough	1	0,3		
	Dyspnoea	5	1,4		
Gastrointestinal disorder	Abdominal pain	2	0,6	2	0,9
	Abnormal faeces	1	0,3	1	0,4
	Constipation	1	0,3	2	0,9
	Diarrhoea	5	1,4		

	Discoloured vomit	1	0,3		
	Faeces discoloured	1	0,3		
	Flatulence	2	0,6	2	0,9
	Gastrointestinal pain	1	0,3	1	0,4
	Nausea			1	0,4
	Regurgitation	1	0,3		
	Vomiting	11	3,0	6	2,7
Skin and subcutaneous tissue disorder	Eczema	2	0,6		
	Erythema	1	0,3	1	0,4
	Nodular rash			1	0,4
	Rash			1	0,4
	Rash erythematous	1	0,3	2	0,9
	Rash macular			1	0,4
	Skin discolouration	5	1,4	2	0,9
	Yellow skin	1	0,3		
Eye disorders	Strabismus	1	0,3	1	0,4
Injury, poisoning and procedural complications	Incorrect route of product administration			1	0,4
Reproductive and breast disorders					
Musculoskeletal and connective tissue disorders	Musculoskeletal stiffness	1	0,3	1	0,4
	Pain in extremity	2	0,6	1	0,4
General disorders					
Injection site reactions	Extensive swelling of vaccinated limb	2	0,6	1	0,4
	Injection site erythema	21	5,8	12	5,3
	Injection site granuloma			1	0,4
	Injection site haematoma			1	0,4
	Injection site induration			10	4,4
	Injection site inflammation	21	5,8	8	3,6
	Injection site pain	24	6,6	6	2,7
	Injection site swelling	26	7,2	12	5,3
	Injection site warmth	14	3,9	7	3,1
Systemic reactions	Asthenia	1	0,3	1	0,4
	Body temperature decreased			1	0,4
	Body temperature fluctuation	1	0,3		0,0
	Body temperature increased	4	1,1	3	1,3
	Crying	48	13,3	21	9,3
	Fatigue	4	1,1	1	0,4
	Hyperpyrexia	1	0,3	1	0,4
	Listless	4	1,1	9	4,0
	Malaise	3	0,8	1	0,4
	Moaning	1	0,3		
	Pain	4	1,1		
	Oedema genital	1	0,3		
	Peripheral swelling	1	0,3		
	Pyrexia	56	15,5	49	21,8
	Screaming	2	0,6	1	0,4
	Swelling	1	0,3		0,0
	Swelling face	1	0,3		
Total		362	100,0	225	100,0

Aappendix 3

Overview of reported non-serious AEFIs per SOC Vaxelis cohort (up to and including June 1019) and Infanrix hexa cohort (up to and including June 2018) vaccination number 1 of the series.

Vaccination number 1 (8 weeks)		Vaxelis cohort		Infanrix hexa cohort	
Systemic Organ Class (SOC)	**Pt**	**N**	**%**	**N**	**%**
infections and infestations	Ear infection	1	0,4		
	Nasopharyngitis			1	0,6
Blood and lymphatic system disorders					
Immune system disorders	Urticaria	1	0,4		
Metabolism and nutrition disorders	Decreased appetite	9	3,8	3	1,9
	Hypophagia	2	0,9		
	Increased appetite			1	0,6
	Thirst decreased			1	0,6
Psychiatric disorders	Anxiety	1	0,4		
	Breath holding	2	0,9	2	1,3
	Feeling jittery			2	1,3
	Insomnia	4	1,7	1	0,6
	Irritability	3	1,3		
	Mood altered	1	0,4		
	Nervousness			1	0,6
	Restlessness	2	0,9		
	Sleep disorder	1	0,4		
Nervous system disorders	Depressed level of consciousness	1	0,4	1	0,6
	Exaggerated startle response	1	0,4		
	Febrile convulsion	1	0,4		
	Hypertonia			1	0,6
	Hyporesponsive to stimuli	1	0,4	1	0,6
	Hypotonia	2	0,9	1	0,6
	Hypotonic-hyporesponsive episode	1	0,4	3	1,9
	Slow response to stimuli	1	0,4		
	Somnolence	7	3,0	13	8,3
Vascular disorders	Pallor	7	3,0	2	1,3
	Livedo reticularis	1	0,4		
	Petechiae			2	1,3
	Vasodilatation			1	0,6
Cardiac disorders	Cardiac murmur			1	0,6
	Cyanosis			1	0,6
respiratory, thoracic and mediastinal disorder	Cough	1	0,4		
Gastrointestinal disorder	Abdominal pain	1	0,4	2	1,3
	Abnormal faeces	1	0,4	1	0,6
	Diarrhoea	3	1,3		
	Faeces discoloured	1	0,4		
	Flatulence			2	1,3
	Gastrointestinal pain	1	0,4	1	0,6
	Regurgitation	1	0,4		
	Vomiting	6	2,6	5	3,2
				1	0,6
Skin and subcutaneous tissue disorder	Eczema	1	0,4		
	Nodular rash			1	0,6

	Rash			1	0,6
	Skin discolouration	5	2,1	1	0,6
	Yellow skin	1	0,4		
Eye disorders	Strabismus	1	0,4	1	0,6
Injury, poisoning and procedural complications	Incorrect route of product administration			1	0,6
Reproductive and breast disorders	Oedema genital	1	0,4		
	Musculoskeletal stiffness	1	0,4	1	0,6
Musculoskeletal and connective tissue disorders	Pain in extremity	2	0,9	1	0,6
General disorders					
Injection site reactions	Extensive swelling of vaccinated limb	1	0,4		
	Injection site erythema	13	5,5	6	3,8
	Injection site haematoma			1	0,6
	Injection site induration			6	3,8
	Injection site inflammation	14	6,0	7	4,5
	Injection site pain	18	7,7	4	2,5
	Injection site swelling	17	7,2	9	5,7
	Injection site warmth	8	3,4	5	3,2
Systemic reactions	Asthenia			1	0,6
	Body temperature fluctuation	1	0,4		
	Body temperature increased	2	0,9	1	0,6
	Crying	32	13,6	16	10,2
	Fatigue	2	0,9	1	0,6
	Hyperpyrexia			1	0,6
	Listless	2	0,9	9	5,7
	Malaise	1	0,4		
	Moaning	1	0,4		
	Pain	1	0,4		
	Peripheral swelling	1	0,4		
	Pyrexia	41	17,4	31	19,7
	Screaming	2	0,9	1	0,6
	Swelling	1	0,4		
Total	Totaal	235	100,0	157	100,0

Appendix 4

Overview of reported non-serious AEFIs per SOC Vaxelis cohort (up to and including June 1019) and Infanrix hexa cohort (up to and including June 2018) vaccination number 2 of the series.

Vaccination number 2 (12 weeks)		Vaxelis cohort		Infanrix hexa cohort	
Systemic Organ Class (SOC)	**Pt**	**N**	**%**	**N**	**%**
infections and infestations					
Blood and lymphatic system disorders					
Immune system disorders					
Metabolism and nutrition disorders	Decreased appetite	3	3,8	1	2,1
Psychiatric disorders	Apathy	1	1,3	1	2,1
	Insomnia	3	3,8	1	2,1
	Restlessness	1	1,3		
Nervous system disorders	Apparent life threatening event			1	2,1
	Depressed level of consciousness			1	2,1
	Drooling	1	1,3		
	Headache			1	2,1
	Hypertonia			1	2,1
	Hypotonia			1	2,1
	Infantile back arching	1	1,3		
	Slow response to stimuli			1	2,1
	Somnolence			1	2,1
	Syncope	1	1,3		
Vascular disorders	Pallor	1	1,3	1	2,1
Cardiac disorders					
respiratory, thoracic and mediastinal disorder					
Gastrointestinal disorder	Abdominal pain	1	1,3		
	Constipation	1	1,3	1	2,1
	Diarrhoea	2	2,5		
	Discoloured vomit	1	1,3		
	Flatulence	1	1,3		
	Nausea			1	2,1
	Vomiting	3	3,8	1	2,1
Skin and subcutaneous tissue disorder	Eczema	1	1,3		
	Erythema	1	1,3	1	2,1
	Rash erythematous	1	1,3	1	2,1
Eye disorders					
Injury, poisoning and procedural complications					
Reproductive and breast disorders					
Musculoskeletal and connective tissue disorders					
General disorders					
Injection site reactions	Extensive swelling of vaccinated limb			1	2,1
	Injection site erythema	6	7,6	4	8,5
	Injection site granuloma			1	2,1
	Injection site induration			3	6,4
	Injection site inflammation	6	7,6	1	2,1
	Injection site pain	6	7,6	2	4,3
	Injection site swelling	7	8,9	3	6,4
	Injection site warmth	6	7,6	2	4,3
Systemic reactions	Asthenia	1	1,3		

	Body temperature decreased			1	2,1
	Body temperature increased	1	1,3	2	4,3
	Crying	8	10,1	3	6,4
	Fatigue	1	1,3		
	Listless	2	2,5		
	Malaise	1	1,3	1	2,1
	Pain	2	2,5		
	Pyrexia	8	10,1	7	14,9
Total	Totaal	79	100,0	47	100,0

Appendix 5

Overview of reported non-serious AEFIs per SOC Vaxelis cohort (up to and including June 1019) and Infanrix hexa cohort (up to and including June 2018) vaccination number 3 of the series.

Vaccination number 3 (16 weeks)		Vaxelis cohort		Infanrix hexa cohort	
Systemic Organ Class (SOC)	Pt	N	%	N	%
infections and infestations	Nasopharyngitis			1	5,3
Blood and lymphatic system disorders					
Immune system disorders					
Metabolism and nutrition disorders	Decreased appetite				
Psychiatric disorders	Insomnia	1	2,8		
Nervous system disorders	Hyporesponsive to stimuli	1	2,8		
	Hypotonia	1	2,8		
	Hypotonic-hyporesponsive episode	2	5,6		
	Petit mal epilepsy	1	2,8		
	Somnolence	3	8,3		
	Syncope	1	2,8		
Vascular disorders	Pallor	1	2,8		
Cardiac disorders					
respiratory, thoracic and mediastinal disorder	Dyspnoea	1	2,8		
Gastrointestinal disorder	Flatulence	1	2,8		
	Vomiting	2	5,6		
Skin and subcutaneous tissue disorder	Petechiae	1	2,8		
	Rash erythematous			1	5,3
	Rash macular			1	5,3
	Skin discolouration			1	5,3
Eye disorders					
Injury, poisoning and procedural complications					
Reproductive and breast disorders					
Musculoskeletal and connective tissue disorders					
General disorders					
Injection site reactions	Extensive swelling of vaccinated limb	1	2,8		
	Injection site erythema	1	2,8	2	10,5
	Injection site induration			1	5,3
	Injection site swelling	1	2,8		
Systemic reactions	Body temperature increased	1	2,8		
	Crying	7	19,4	2	10,5
	Malaise	1	2,8		
	Pain	1	2,8		
	Pyrexia	6	16,7	10	52,6
	Swelling face	1	2,8		
Total	Totaal	36	100,0	19	100,0

Appendix 6

Overview of reported non-serious AEFIs per SOC Vaxelis cohort (up to and including June 1019) and Infanrix hexa cohort (up to and including June 2018) vaccination number 9 of the series.

Vaccination number missing		Vaxelis cohort		Infanrix hexa cohort	
Systemic Organ Class (SOC)	**Pt**	**N**	**%**	**N**	**%**
infections and infestations					
Blood and lymphatic system disorders					
Immune system disorders					
Metabolism and nutrition disorders					
Psychiatric disorders	Irritability			1	50
Nervous system disorders					
Vascular disorders					
Cardiac disorders	Heart rate increased	1	11,1		
respiratory, thoracic and mediastinal disorder	Dyspnoea	1	11,1		
Gastrointestinal disorder					
Skin and subcutaneous tissue disorder					
Eye disorders					
Injury, poisoning and procedural complications					
Reproductive and breast disorders					
Musculoskeletal and connective tissue disorders					
General disorders					
Injection site reactions	Injection site erythema	1	11,1		
	Injection site inflammation	1	11,1		
	Injection site swelling	1	11,1		
Systemic reactions	Crying	1	11,1		
	Fatigue	1	11,1		
	Hyperpyrexia	1	11,1		
	Pyrexia	1	11,1	1	50
Total	Totaal	9		2	