Overview reported AEFIs Vaxelis® compared to Infanrix hexa® at infant age (second overview)

Introduction

At the end of 2018 in the National Immunization Program of the Netherlands (RVP) the diphtheria-pertussis-tetanus-IPV-HiB-hepB vaccine Infanrix hexa® was replaced by Vaxelis®. Vaxelis® has been licensed since February 15, 2016 [1]. As standard in the current legislation it is a drug under additional monitoring which implies that the Netherlands Pharmacovigilance Center Lareb will closely monitor Vaxelis® in the first two years after introduction in the RVP on the basis of spontaneous reports.

Until 2018, Infanrix hexa® was included 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]. Infants born before December 1, 2018, who started the primary series with Infanrix hexa®, completed the primary series and first booster vaccination with Infanrix hexa®. However, infants born on December 1, 2018 or later, started the primary series and first booster vaccination with Vaxelis® [3].

In the Netherlands, at the age of 2, 4 and 11 months the administration of DTP-IPV-HiB-HepB vaccine is combined with administration of a pneumococcal vaccination (Synflorix®) in the contralateral leg (Table1).
In December 2019, maternal pertussis vaccination, using dTaP, was introduced in the RVP. For infants who are exposed during pregnancy to maternal pertussis vaccination, the vaccination schedule is modified. Infants from mothers who did not receive the pertussis vaccination during pregnancy and/or infants who are born within 2 weeks after the mother received the vaccination will be vaccinated according to a 2-3-5-11-months schedule. In anticipation of the introduction of maternal pertussis vaccination, some women already have been vaccinated on their own initiative in 2019, and some of these infants are already vaccinated according to the new schedule.

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

Vaccination schedule	Age	Until December 1, 2018 (old schedule)	After December 1, 2018 (old schedule)	After January 1, 2020* (maternal pertussis) (new schedule)
1	8 weeks	Infanrix hexa® + Synflorix®	Vaxelis® + Synflorix®	
2 (A)	12 weeks	Infanrix hexa®	Vaxelis®	Vaxelis® + Synflorix®
3	16 weeks	Infanrix hexa® + Synflorix®	Vaxelis® + Synflorix®	
(B)	20 weeks			Vaxelis® + Synflorix®
4 (C)	11 months	Infanrix hexa® + Synflorix®	Vaxelis® + Synflorix®	Vaxelis® + Synflorix®

* December 2019 Maternal Pertussis prophylaxis was introduced in the RVP. The injection number 1 to 4 represents the old classical schedule and the injection number A to C represents the new schedule.

To perform this monitoring task, spontaneous reports of the birth cohort of children born between 1-12-2018 and 1-12-2019 (Vaxelis cohort) will be compared with spontaneous reports of the birth cohort of children born between 1-12-2017 and 1-12- 2018 (Infanrix hexa cohort).

The monitoring of Vaxelis is performed on the basis of the following research questions:
1. Are there more reports and/or 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 reports of 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?

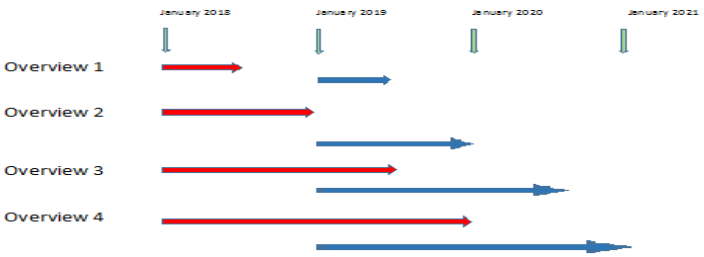

Figure 1 Comparable reporting periods in time for the overviews. Red arrows represent the Infanrix hexa cohort and the blue arrows the Vaxelis cohort.

The reports from the Vaxelis cohort will be compared with the reports from the Infanrix hexa cohort over a comparable period a year earlier. A total of four overviews will be made. Figure 1 provides an overview of the comparable periods over time.

- The first overview is already published and related 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 (6-month period) [4].
- Overview 2 will be presented in the present report and 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 (12 month period).
- 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 (18 month period).
- 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 (24 month period).

The two cohorts and the comparison of these cohorts are followed under the provisional assumption that both cohorts are the same size and that the number of vaccinations per vaccination moment is comparable. Information about the actual number of vaccinated children per vaccination moment per cohort during the follow-up phase is lacking. Therefore, no reporting rates and rate ratios are calculated in overview 1 to 3. After the follow-up phase, the number of vaccinated children per vaccination moment per cohort will be requested. In the final fourth overview, 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 of these birth cohorts. 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

For the second overview spontaneous reports were selected after administration of Vaxelis® from children born between December 1, 2018 and December 1, 2019, which were received in the period from January 1, 2019 to January 1, 2020 (Vaxelis cohort). Furthermore, spontaneous reports after the administration of Infanrix-hexa® were selected from children born between December 1, 2017 and December 1, 2018, which were received in the period from January 1, 2018 to January 1, 2019 (Infanrix-hexa cohort). From both cohorts,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 spontaneous reports and reported AEFIs of Vaxelis® from children born between December 1, 2018 and December 1, 2019, which were received in the period from January, 1 2019 to January 1, 2020 (Vaxelis cohort) and spontaneous reports and reported AEFIs of Infanrix hexa® from children born between December 1, 2017 and December 1, 2018, which were received in the period from January, 1 2018 to January 1, 2019 (Infanrix hexa cohort).

Vaccination schedule (numbers old schedule*)	Infanrix hexa cohort		Vaxelis cohort (no maternal pertussis)		Vaxelis cohort (maternal pertussis)		Vaxelis cohort (total)	
	Number reports	Number AEFIs	Number reports	Number AEFIs	Number reports	Number AEFIs	Number reports	Number AEFIs
8 weeks (1)	162 (50.6%)	423 (40.9%)	152 (46.8%)	521 (39.4%)			152 (43.8%)	521 (37.0%)
12 weeks (2/A)	53 (16.6%)	145 (14.0%)	82 (25.2%)	307 (23.2%)	18*** (81.8%)	57 (68.7%)	100 (28.8%)	364 (25.9%)
16 weeks (3)	81 (25.3%)	351 (33.9%)	78 (24.0%)	411(31.0%)			78 (22.5%)	411 (29.2%)
20 weeks (B)					3 (13.6%)	18 (21.7%)	3 (0.9%)	18 (1.3%)
11 months (4/C)**	24 (7.5%)	116 (11.2%)	13 (4.0%)	85 (6.4%)	1 (4.5%)	8 (9.6%)	14 (4.0%)	93 (6.6%)
Total	320 (100%)	1035 (100%)	325 (100%)	1324 (100%)	22 (100%)	83 (100%)	347(100%)	1407(100%)

* The numbers 1 to 4 of the vaccination schedule corresponds with the vaccination numbers 1 to 4 of the old classical schedule and the letters A to C with the vaccination moments in the new schedule after maternal pertussis prophylaxis. Only a few children in the Vaxelis cohort are vaccinated conform the new schedule..

** The number of reports after vaccination moments 11 months is still limited, because only a limited number of children were old enough to have reached the age for all vaccination moments.

*** One child protected by maternal pertussis prophylaxis followed the old schedule and reported an adverse reaction after the second vaccination

Table 2 provides an overview of the number of reports and the number of reported AEFIs from the Vaxelis and Infanrix hexa cohort. From the Vaxelis cohort 347 reports have been received. Of these reports, the brand name of the vaccine was confirmed in 297 reports by means of the batch number (85.6%). In the Infanrix hexa cohort 320 reports have been received (265 confirmed cases based on the batch number, 82.8%) in the comparable period one year earlier, a difference of 8.4%. In particular after the second vaccination, AEFIs were more frequently reported in the Vaxelis cohort. A report may contain multiple AEFIs. The total number of reported AEFIs in the Vaxelis cohort is higher compared to the number of AEFIs in the Infanrix hexa cohort (1,407 versus 1,035, a difference of 35.9%).

Serious reports and reported AEFIs

Table 3 shows the number of serious and non-serious reports per vaccination of the series. According to the Council for International Organizations of Medical Sciences criteria (CIOMS criteria) for seriousness, 7.1% of the Vaxelis® cohort are serious and 9.4% of the Infanrix hexa cohort. In the Vaxelis cohort as well in the Infanrix hexa cohort most serious reports were reported after the first administration (vaccination number 1) at approximately the age of 8 weeks (9.2% vs. 10.5%). 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 schedule (numbers old schedule)	Infanrix hexa® cohort		Vaxelis cohort (no maternal pertussis)		Vaxelis cohort (maternal pertussis)		Vaxelis cohort (total)	
	serious	Non-serious	serious	Non-serious	Serious	Non-serious	Serious	Non-serious
8 weeks (1)	17 (10.5%)	145 (89.5%)	14 (9.2%)	138 (90.8%)			14 (9.2%)	138 (90.8%)
12 weeks (2/A)	7 (13.2%)	46 (86.8%)	3 (3.7%)	79 (96.3%)		17	3 (3.0%)	96 (97.0%)
16 weeks (3)	5 (6.2%)	76 (93.8%)	6 (7.7%)	72 (92.3%)			6 (7.7%)	72 (92.3%)
20 weeks (B)						4		4 (100%)
11 months (4/C)	1 (4.2%)	23 (95.8%)		13 (100%)		1		14 (100%)
total	30 (9.4%)	290(90.6%)	23 (7.1%)	302(92.9%)		22	23 (6.6%)	324 (93.4%)

* During vaccination numbers 1, 3 and 4 old schedule, both Vaxelis® and Infanrix hexa® are often co-administered with Synflorix® in the contralateral leg. In children born after maternal pertussis prophylaxis following the new schedule, the regular vaccination schedule is Vaxelis® in combination with Synflorix®.

Serious reports of death

Three deaths were reported in the Vaxelis cohort (no maternal pertussis). In two cases it concerned a death after the first administration of Vaxelis® in combination with Synflorix®. In both cases autopsy has been performed. One infant died as a result of fulminant sepsis 9 days after the vaccination and the other infant as a result of SIDS 2.5 days after the vaccination. Based on the information provided by the reporter, the result of the autopsy, and current knowledge in the literature, a relationship between the death of the infant and the administered vaccines was considered unlikely in either case. The third reported death occurred 3 days after the third administration of Vaxelis® in combination with Synflorix®. No autopsy was performed. Based on circumstantial findings, the pediatrician concluded that the infant died as a result of SIDS. Based on the information provided by the reporter and current knowledge in the literature, there are no aspects that supported a causal relationship; therefore, a causal relationship was considered unlikely. These conclusions were endorsed by the external independent Clinical Advisory Board of the Netherlands Pharmacovigilance Centre Lareb (KAR).

In the Infanrix hexa® cohort, there was one report of death in the comparable period a year earlier. It concerned a report of an infant who died 3 days after vaccination due to intussusception with fatal intestinal bleeding. Based on the information provided by the reporter and absence of supportive knowledge in the literature, a relationship between the death of the infant and the administered vaccines was considered unlikely.

Other serious reports

The other 20 serious reports in the Vaxelis cohort (no maternal pertussis) concerned reports of hospital admissions (18x) and serious other medically important condition (2x). Twelve of these events occurred after the first vaccination, three after the second and five after the third vaccination.

Eleven of the hospital admissions were related to short-lasting events that occurred a few hours (4-8 hours) after vaccination. In these cases, pallor, hypotonia, and hyporesponsivity were often reported. These events are known in the literature as Hypotonic Hyporesponsive Event (HHE[1]). Infants with an HHE are often admitted to the hospital for 24-hour monitoring. Further investigations and monitoring usually show no abnormalities. One child with HHE was not admitted to the hospital, but the report was qualified as a serious other medically important condition.

One report of hospitalization concerned a recurring short-lasting episode (5-10 minutes) of a collapse-like event of crying, turning away of the eyes, breath holding and pallor. The symptoms were eventually diagnosed by the reporting pediatrician as breath holding spells.

Three reports concerned a hospital admission on suspicion of a convulsion. One of these reports concerned an event of dyspnea, fever and shaking a few hours after the first vaccination. Blood, urine tests and EEG showed no abnormalities. The second report concerned a hospital admission of recurrent convulsion, followed by crying. This infant recovered within 2 to 3 hours after hospitalization and after the administration of paracetamol. The third report described a convulsion (apnea, foaming at the mouth and hypertonia) 6 days after the first vaccination. Brain scan showed no abnormalities.

One report concerned a premature born infant with a hospital admission for a necrotizing enterocolitis after the 1st administration of Vaxelis®, Synflorix® and rotavirus-vaccine at the age of 9 weeks.

[1] Not to be confused with the abbreviation HHE in pediatric neurology, where the term HHE stands for hemiconvulsion-hemiplegia epilepsy syndrome.

One report concerned a hospital admission for a common cold 4-7 days after the second vaccination.
There was a report of a hospital admission of urinary tract abnormalities and a urinary tract infection of an infant.
One serious (other medically important condition) report concerned a report of apnea (3 times) 3 hours after the administration of Vaxelis® and Synflorix®. The infant was monitored in the hospital for 2.5 hours, no abnormalities were found.

The 29 serious reports in the Infanrix hexa cohort concern hospital admission (n=27) and serious life-threatening event (n=2). Seventeen of these events occurred after the first vaccination, seven after the second and five after the third vaccination.
Eleven of the hospital admissions were related to short-lasting events that occur a few hours (4-8 hours) after vaccination. One report concerned an HHE, reported as a live threatening event without hospital admission. Two reports of hospital admission concerned reports of syncope within minutes after vaccination.
Two hospital admissions concerned injection site reactions. One infant developed an injection site abscess with surgical drainage, 11 days after the vaccination. Culture showed a Streptococcus haemolyticus group A. Another infant developed an extensive swelling of the vaccinated limb (ELS) after the third vaccination.
Three hospital admissions were related to suspicion of a convulsion. One time it concerned an infant with hypertonia and drowsiness (reported as postictal) possibly caused by choking one day after the first vaccination. Another report concerned a non-febrile convulsion seven hours after the first vaccination. The third hospital admission concerned a child with a convulsion four hours after the second vaccination.
Four hospital admissions and one live threatening event were reports of possible respiratory disorders. Two times it concerned apnea. One time it concerned an infant with pyrexia, hypotonia and apnea ten hours after the third vaccination. The other report of apnea concerned an infant born prematurely who developed apnea, bradycardia and oxygen saturation decrease eight hours after vaccination in the hospital. The infant recovered after resuscitation. There were three reports of dyspnea. Two times it concerned choking / breathing difficulties with excessive salivation after vaccination.
One infant was briefly admitted to the hospital for observation in connection with pyrexia (40° Celsius) after the first vaccinations. Blood and urine tests showed no evidence of infection. One infant was admitted for fever, rash, and peripheral swelling occurring ten hours after the first vaccinations. The child was treated with an antihistamine and recovered. One infant was admitted to the hospital due to persistent gastroesophageal reflux developed 4 to 5 days after the first vaccinations. One child was admitted to the hospital for idiopathic thrombocytopenic purpura (ITP) with petechiae three days after the second vaccination. Viral infections were excluded. One child was admitted to the hospital for pyrexia, leucopenia and aphthae after the second vaccination.

Non-serious AEFIs
Appendix 2 provides an overview of all reported non-serious AEFIs (coded PT) per System Organ Class (SOC) per cohort. In the Vaxelis cohort, 1,343 non-serious AEFIs were reported in the period January 1, 2019 until December 31, 2019. The Infanrix hexa cohort included 946 non-serious AEFIs, reported in the comparable period one year earlier (January 1, 2018 until December 31, 2018). The number of reports and the number of AEFIs differ per vaccination moment at infant age. The vast majority is reported after administration of the first vaccination at the age of two months. The type of reported AEFIs also differs per vaccination moment. For this reason, AEFIs are broken down by vaccination moment. Appendix 3 to 6 provides an overview of the reported AEFIs per vaccinationmoment of the old schedule. After all vaccination moments, more AEFIs are reported after administration of Vaxelis® (/ Synflorix®) than after administration of Infanrix hexa® (/ Synflorix®).
Appendix 7 provides an overview of the reported AEFIs of children who are vaccinated according to the new vaccination schedule, i.e. after the introduction of maternal pertussis vaccination. The reported AEFIs 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 of the Vaxelis cohort (22 reports). As these children follow a new vaccination schedule, the reports and reported AEFIs are difficult to compare with the Infanrix hexa cohort

In the underlying text the side effects at different vaccination moments are discussed, we have limited ourselves to children whose mother did not receive a pertussis vaccine (the old schedule).

AEFIs after the first vaccination (Appendix 3)
After the first administration 494 non-serious AEFIs have been reported in the Vaxelis cohort (138 reports) against 355 AEFIs in the Infanrix hexa cohort (145 reports).
Notable is the difference in the number of reported injection site reactions (Vaxelis cohort 145x versus Infanrix hexa cohort 87x). It concerns in particular reports of injection site swelling, injection site redness, injection site pain and injection site inflammation, and extensive swelling of the vaccinated limb. In the Vaxelis cohort there are 43 reports (31.2%) with one or more injection site reactions compared to 30 reports of one or more injection site reactions in the Infanrix hexa cohort (20.7%).

Also crying, including screaming and high pitch crying, has been more frequently reported after administration of Vaxelis® / Synflorix® (n=65) compared to Infanrix hexa® / Synflorix® (n=39). Crying is often reported in combination with other AEFIs. In the Vaxelis cohort, 61 reports of crying (93.8%) contained one or more other AEFIs , such as fever / elevated body temperature 39x (60.0%) and injection site reaction 20x (30.8%). In the Infanrix hexa cohort, 33 reports of crying (84.6%) contained one or more other AEFIs, such as fever / elevated body temperature 27x (69.2%) and injection site reaction 8x (20.5%).
Furthermore, skin discoloration was more frequently reported after administration of Vaxelis® / Synflorix® (n=10) compared to Infanrix hexa® / Synflorix® (n= 5).

AEFIs after the second vaccination (Appendix 4)
After the second administration 343 non-serious AEFIs have been reported in the Vaxelis cohort (79 reports) against 131 AEFIs in the Infanrix hexa cohort (46 reports).
Notable is the difference in the number of reported injection site reactions (Vaxelis cohort 103x versus Infanrix hexa cohort 35x). In the Vaxelis cohort there are 29 reports (36.7%) with one or more injection site reactions compared to 12 reports with one or more injection site reactions in the Infanrix hexa cohort (26.1%).
Also crying, including screaming and high pitch crying, has been more frequently reported after administration of Vaxelis® / Synflorix® (n=51) compared to Infanrix hexa® / Synflorix® (n=11).
Other notable differences in reports are fever / increased body temperature (41x versus 27x), drinking less well (14x versus 5x), disturbances of the sleep rhythm (insomnia 9x versus 2x; somnolence 8x versus 2x) and gastrointestinal complaints (28x versus 10x).
Furthermore, skin discoloration was more frequently reported after administration of Vaxelis® / Synflorix® compared to Infanrix hexa® / Synflorix® (8x versus 1x).

AEFIs after the third vaccination (Appendix 5)
After the third administration 398 non-serious AEFIs have been reported in the Vaxelis cohort (72 reports) against 213 AEFIs in the Infanrix hexa cohort (76 reports).
Notable is the difference in the number of reported injection site reactions (Vaxelis cohort 110x versus Infanrix hexa cohort 36x). In the Vaxelis cohort there are 22 reports (30.6%) with one or more injection site reactions compared to 7 reports with one or more injection site reactions in the Infanrix hexa cohort (9.2%).
The large number of reports of crying in the Vaxelis cohort is striking. In 52 out of the 72 Vaxelis reports, crying was reported (72.2%), versus none in the Infanrix hexa reports.
In the Vaxelis cohort as well as in the Infanrix hexa cohort some non-serious reports contain symptoms that meet the definition of HHE. (Vaxelis 6x versus Infanrix hexa 3x). Furthermore two reports in the Vaxelis cohort were coded as syncope.

AEFIs after the fourth vaccination (Appendix 6)
After the fourth administration 85 non-serious AEFIs have been reported in the Vaxelis cohort (13 reports) against 114 AEFIs in the Infanrix hexa cohort (23 reports).
The reported AEFIs after the fourth vaccination 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 (Vaxelis cohort children born between December 1 and December 31, 2018 and Infanrix hexa cohort born between December 1, 2017 and February 2, 2018).

Other sources of information

SmPC
The SmPC from Vaxelis® was first published on February 2, 2016 and was last updated on February 19, 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® [5]. In particular, AEFIs such as HHE, collapse, convulsions, febrile convulsions, urticaria, angioedema and facial oedema are not listed in section 4.8 of the Vaxelis® SmPC, but as AEFIs that have been reported in post-marketing surveillance.

Discussion and conclusion

This report is the second overview of a total of four semi-annual reports in which the first birth cohort that is vaccinated with Vaxelis® will be compared to the last birth cohort which was vaccinated with Infanrix hexa®. The comparison of these cohorts was made under the provisional assumption that both cohorts are the same size and that the number of vaccinations per vaccination moment is comparable, and that the reporting behavior of reporters and the reporting procedure are unchanged.

In the period January 1, 2019 - December 31, 2019 Pharmacovigilance Centre Lareb received 8.4% 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 - December 31, 2018). In comparison with the first overview that is related to the first half year, this difference in the number of reports decreased from 25.5% to 8.4%.
In the Vaxelis cohort, 35.9% more AEFIs were reported compared to the Infanrix hexa cohort. In comparison with the first overview that is related to the first half year, this difference in the number of AEFIs decreased from 48% to 35.9%.

In the Vaxelis cohort 23 reports out of 347 reports (7.1%) were serious and in the Infanrix hexa 30 out of 320 (9.4%). In comparison to the first overview the relative number of serious reports in the Vaxelis cohort has decreased from 8.8% to 7.1%. The relative number of serious reports in the Infanrix hexa cohort remained about the same compared to the first overview.
In both cohorts, most serious reports were reported after the first vaccinations, mainly hospital admissions related to short-lasting events of pallor, hypotonia, and hyporesonsivity. These events are known in the literature as Hypotonic Hyporesponsive Event (HHE).

More non-serious reports were reported in the Vaxelis cohort than in the Infanrix hexa cohort (324 versus 290) and more non-serious AEFIs were reported (1343 versus 946). The majority of these non-serious AEFIs are well known AEFIs. The number of reports of injection site reactions, crying and skin discoloration were higher in the Vaxelis cohort compared to the Infanrix hexa cohort. The differences in the number of reports of injection site reactions and crying may indicate a difference in reactogenicity between Vaxelis® and Infanrix hexa®. However, no firm conclusion can be drawn based on the reporting. This will be further monitored in the following reports.

The second analysis of the reports of AEFIs 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://www.ema.europa.eu/en/documents/product-information/infanrix-hexa-epar-product-information_en.pdf
4. https://databankws.lareb.nl/Downloads/Signals_2019_overview%20AEFIs%20Vaxelis%20compared%20Infanrix%20hexa.pdf
5. https://www.ema.europa.eu/en/documents/variation-report/infanrix-hexa-h-c-296-p46-128-epar-assessment-report_en.pdf

This signal has been raised on June 3, 2020. 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 (January 1, 2019 up to and including December 31, 2019) and Infanrix hexa cohort (January 1, 2018 up to and including December 31, 2018).`

		Vaxelis		Infanrix hexa	
Systemic Organ Class (SOC)	Pt	N	%	N	%
infections and infestations	Ear infection	1	0,1		
Blood and lymphatic system disorders	Anaemia	1	0,1		
Immune system disorders	Urticaria	3	0,2		
Metabolism and nutrition disorders	Decreased appetite	36	2,7	21	2,2
	Fluid intake reduced	2	0,1		
	Hypophagia	4	0,3	1	0,1
	Increased appetite	1	0,1	6	0,6
	Poor feeding infant			2	0,2
	Thirst decreased			1	0,1
	Weight gain poor	1	0,1		
Psychiatric disorders	Aberrant motor behaviour	1	0,1		
	Abnormal behaviour	4	0,3		
	Agitation	1	0,1	1	0,1
	Anxiety	3	0,2		
	Apathy	1	0,1	3	0,3
	Behaviour disorder	1	0,1		
	Breath holding	4	0,3	2	0,2
	Feeling jittery			2	0,2
	Hypersomnia	5	0,4	3	0,3
	Insomnia	18	1,3	10	1,1
	Irritability	4	0,3	1	0,1
	Mood altered	1	0,1		
	Nervousness			1	0,1
	Panic reaction	1	0,1		
	Poor quality sleep	1	0,1	2	0,2
	Restlessness	11	0,8	4	0,4
	Sleep disorder	3	0,2		
	Somnolence	39	2,9	21	2,2
	Staring	1	0,1	1	0,1
Nervous system disorders	Apparent life threatening event			1	0,1
	Depressed level of consciousness	1	0,1	4	0,4
	Drooling	1	0,1		
	Dyskinesia	1	0,1	1	0,1
	Dysphonia	1	0,1		
	Exaggerated startle response	1	0,1		
	Febrile convulsion	3	0,2	4	0,4
	Fontanelle bulging			2	0,2
	Gait disturbance	1	0,1		
	Headache		0,0	2	0,2
	Hypertonia	6	0,4	2	0,2
	Hyporesponsive to stimuli	5	0,4	6	0,6
	Hypotonia	10	0,7	10	1,1
	Hypotonic-hyporesponsive episode	13	1,0	15	1,6
	Infantile back arching	2	0,1		
	Loss of consciousness	2	0,1	1	0,1
	Muscle twitching	1	0,1		
	Myoclonus			1	0,1
	Opisthotonus	2	0,1		
	Petit mal epilepsy	1	0,1		
	Poor sucking reflex	1	0,1		
	Posture abnormal	1	0,1	1	0,1
	Presyncope	1	0,1		
	Seizure	1	0,1		
	Slow response to stimuli	1	0,1	2	0,2
	Syncope	6	0,4	1	0,1
	Tremor	2	0,1		
	Unresponsive to stimuli	1	0,1	2	0,2
Vascular disorders	Livedo reticularis	2	0,1		
	Pallor	20	1,5	16	1,7
	Petechiae	7	0,5	10	1,1
	Purpura			1	0,1
	Vasodilatation			1	0,1
Cardiac disorders	Cardiac murmur			1	0,1
	Cyanosis	2	0,1	1	0,1
	Heart rate increased	1	0,1		
	Tachycardia			2	0,2
respiratory, thoracic and mediastinal disorder	Apnoeic attack	2	0,1	1	0,1
	Catarrh			1	0,1
	Choking	1	0,1		
	Cough	4	0,3	1	0,1
	Dyspnoea	16	1,2	3	0,3
	Irregular breathing			2	0,2
	Nasal congestion	1	0,1		
	Nasopharyngitis	3	0,2	3	0,3
	Productive cough	1	0,1		
	Respiration abnormal	2	0,1		
	Respiratory disorder	1	0,1		
	Respiratory rate increased	1	0,1	2	0,2
	Rhinorrhoea	2	0,1		
Gastrointestinal disorder	Abdominal pain	9	0,7	4	0,4
	Abnormal faeces	2	0,1	2	0,2
	Constipation	6	0,4	3	0,3
	Diarrhoea	13	1,0	12	1,3
	Discoloured vomit	1	0,1		
	Faecal volume decreased	1	0,1		
	Faeces discoloured	3	0,2		
	Flatulence	5	0,4	4	0,4
	Frequent bowel movements			2	0,2
	Gastrointestinal pain	3	0,2	2	0,2
	Gastrointestinal viral infection			2	0,2

	Gastrooesophageal reflux disease	2	0,1		
	Haematochezia	1	0,1	2	0,2
	Nausea	4	0,3	1	0,1
	Regurgitation	2	0,1		
	Retching	2	0,1	1	0,1
	Salivary hypersecretion	1	0,1		
	Vomiting	36	2,7	30	3,2
	Vomiting projectile	1	0,1	1	0,1
Skin and subcutaneous tissue disorder	Dermatitis atopic	1	0,1		
	Eczema	7	0,5	2	0,2
	Erythema	10	0,7	6	0,6
	Erythema infectiosum			2	0,2
	Erythema multiforme			2	0,2
	Nodular rash			1	0,1
	Photosensitivity reaction	1	0,1		
	Pruritus	1	0,1		
	Rash	10	0,7	6	0,6
	Rash erythematous	2	0,1	6	0,6
	Rash generalised	4	0,3	2	0,2
	Rash macular	1	0,1	8	0,8
	Rash maculo-papular	3	0,2		
	Rash papular	6	0,4	1	0,1
	Rash pruritic	1	0,1	1	0,1
	Skin discolouration	25	1,9	13	1,4
	Skin warm	1	0,1		
	Subcutaneous haematoma	1	0,1		
	Yellow skin	2	0,1		
Eye disorders	Eye inflammation			4	0,4
	Eye movement disorder	1	0,1	2	0,2
	Eye swelling	1	0,1		
	Strabismus	1	0,1	1	0,1
Injury, poisoning and procedural complications	Incorrect route of product administration		0,0	1	0,1
Reproductive and breast disorders	Penile erythema	1	0,1		
	Penile swelling	1	0,1		
Musculoskeletal and connective tissue disorders	Muscle tightness	1	0,1		
	Musculoskeletal stiffness	2	0,1	1	0,1
	Pain in extremity	8	0,6	4	0,4
General disorders	Extensive swelling of vaccinated limb	11	0,8	2	0,2
Injection site reactions	Injection site abscess			3	0,3
	Injection site bruising	1	0,1		
	Injection site discharge	1	0,1	2	0,2
	Injection site discolouration	6	0,4	4	0,4
	Injection site erythema	80	6,0	56	5,9
	Injection site granuloma			1	0,1
	Injection site haematoma	2	0,1	1	0,1
	Injection site haemorrhage	4	0,3	2	0,2
	Injection site induration	9	0,7	24	2,5
	Injection site inflammation	70	5,2	47	5,0
	Injection site nodule	4	0,3	6	0,6
	Injection site pain	75	5,6	40	4,2
	Injection site pruritus			5	0,5
	Injection site rash	2	0,1	3	0,3
	Injection site reaction			3	0,3
	Injection site scar	1	0,1		
	Injection site swelling	82	6,1	52	5,5
	Injection site urticaria	1	0,1		
	Injection site warmth	57	4,2	25	2,6
	Lymphadenopathy	1	0,1		
	Vaccination site warmth	1	0,1		
Systemic reactions	Asthenia	1	0,1	1	0,1
	Body temperature decreased			3	0,3
	Body temperature fluctuation	1	0,1		
	Body temperature increased	15	1,1	9	1,0
	Chills	1	0,1		
	Crying	169	12,6	82	8,7
	Developmental delay	1	0,1		
	Fatigue	12	0,9	6	0,6
	High-pitched crying	1	0,1		
	Hyperhidrosis	1	0,1	1	0,1
	Hyperpyrexia	7	0,5	7	0,7
	Lip swelling	1	0,1		0,0
	Listless	20	1,5	17	1,8
	Malaise	11	0,8	5	0,5
	Moaning	8	0,6	4	0,4
	Oedema genital	1	0,1		0,0
	Oedema peripheral	3	0,2		0,0
	Pain	16	1,2	5	0,5
	Peripheral swelling	2	0,1	3	0,3
	Pyrexia	187	13,9	212	22,4
	Screaming	5	0,4	1	0,1
	Swelling	1	0,1		
	Swelling face	2	0,1		
	Swollen tongue	1	0,1		
renal and urinary tract disorder	Chromaturia			1	0,1
	Micturition disorder	1	0,1		
	Micturition frequency decreased	2	0,1		
	Ureteric dilatation	1	0,1		
	Urinary tract infection			2	0,2
ear and labyrinth disorder	Hyperacusis	1	0,1		
Total		1343	100,0	946	100,0

Aappendix 3

Overview of reported non-serious AEFIs per SOC Vaxelis cohort (January 1, 2019 up to and including December 31, 2019) and Infanrix hexa cohort (January 1, 2018 up to and including December 31, 2018) of vaccination number 1 of the old schedule

		Vaxelis		Infanrix hexa	
Systemic Organ Class (SOC)	**Pt**	**N**	**%**	**N**	**%**
infections and infestations	Ear infection	1	0,2		
Blood and lymphatic system disorders	Anaemia	1	0,2		
Immune system disorders	Urticaria	1	0,2		
Metabolism and nutrition disorders	Decreased appetite	14	2,8	6	1,7
	Hypophagia	3	0,6	1	0,3
	Increased appetite	1	0,2	1	0,3
	Poor feeding infant			2	0,6
	Thirst decreased			1	0,3
	Weight gain poor	1	0,2		
Psychiatric disorders	Aberrant motor behaviour	1	0,2		
	Abnormal behaviour	2	0,4		
	Anxiety	2	0,4		
	Behaviour disorder	1	0,2		
	Breath holding	3	0,6	2	0,6
	Feeling jittery			2	0,6
	Hypersomnia	3	0,6	1	0,3
	Insomnia	5	1,0	2	0,6
	Irritability	3	0,6		
	Mood altered	1	0,2		
	Nervousness			1	0,3
	Panic reaction	1	0,2		
	Poor quality sleep	1	0,2		
	Restlessness	3	0,6	1	0,3
	Sleep disorder	1	0,2		
	Somnolence	14	2,8	15	4,2
	Staring	1	0,2		
Nervous system disorders	Depressed level of consciousness	1	0,2	2	0,6
	Dyskinesia	1	0,2	1	0,3
	Dysphonia	1	0,2		
	Exaggerated startle response	1	0,2		
	Febrile convulsion			1	0,3
	Headache			1	0,3
	Hypertonia			1	0,3
	Hyporesponsive to stimuli	3	0,6	3	0,8
	Hypotonia	6	1,2	4	1,1
	Hypotonic-hyporesponsive episode	5	1,0	7	2,0
	Infantile back arching				
	Loss of consciousness	1	0,2	1	0,3
	Myoclonus			1	0,3
	Poor sucking reflex	1	0,2		
	Posture abnormal			1	0,3
	Seizure	1	0,2		
	Slow response to stimuli	1	0,2		
	Syncope	2	0,4	1	0,3
	Unresponsive to stimuli	1	0,2		
Vascular disorders	Livedo reticularis	2	0,4		
	Pallor	14	2,8	8	2,3
	Petechiae	3	0,6	1	0,3
	Vasodilatation			1	0,3
Cardiac disorders	Cardiac murmur			1	0,3
	Cyanosis	2	0,4	1	0,3
respiratory, thoracic and mediastinal disorder	Apnoeic attack			1	0,3
	Catarrh			1	0,3
	Choking	1	0,2		
	Cough	1	0,2		
	Dyspnoea	5	1,0	1	0,3
	Nasopharyngitis			1	0,3
	Respiration abnormal	2	0,4		
	Respiratory disorder	1	0,2		
Gastrointestinal disorder	Abdominal pain	3	0,6	2	0,6
	Abnormal faeces	2	0,4	2	0,6
	Constipation	1	0,2	1	0,3
	Diarrhoea	5	1,0	4	1,1
	Faeces discoloured	1	0,2		
	Flatulence	1	0,2	2	0,6
	Frequent bowel movements				
	Gastrointestinal pain	3	0,6	2	0,6
	Gastrooesophageal reflux disease	2	0,4		
	Haematochezia	1	0,2		
	Nausea	2	0,4		
	Retching			1	0,3
	Salivary hypersecretion	1	0,2		
	Vomiting	8	1,6	11	3,1
	Vomiting projectile	1	0,2	1	0,3
Skin and subcutaneous tissue disorder	Eczema	2	0,4		
	Erythema	2	0,4		
	Nodular rash			1	0,3
	Rash	1	0,2	3	0,8
	Rash erythematous	1	0,2		
	Rash generalised	1	0,2	1	0,3
	Rash macular			1	0,3
	Rash maculo-papular	1	0,2		

	Rash papular	1	0,2	1	0,3
	Rash pruritic	1	0,2	1	0,3
	Skin discolouration	10	2,0	5	1,4
	Yellow skin	2	0,4		
Eye disorders	Eye movement disorder	1	0,2		
	Eye swelling	1	0,2		
	Strabismus	1	0,2	1	0,3
Injury, poisoning and procedural complications	Incorrect route of product administration			1	0,3
Reproductive and breast disorders	Penile erythema	1	0,2		
	Penile swelling	1	0,2		
Musculoskeletal and connective tissue disorders	Musculoskeletal stiffness	1	0,2	1	0,3
	Pain in extremity	2	0,4	2	0,6
General disorders	Extensive swelling of vaccinated limb	3	0,6		
Injection site reactions	Injection site bruising	1	0,2		
	Injection site discharge	1	0,2	1	0,3
	Injection site discolouration			2	0,6
	Injection site erythema	27	5,5	14	3,9
	Injection site haematoma	2	0,4	1	0,3
	Injection site haemorrhage	1	0,2		
	Injection site induration	2	0,4	8	2,3
	Injection site inflammation	26	5,3	18	5,1
	Injection site nodule			1	0,3
	Injection site pain	31	6,3	12	3,4
	Injection site pruritus			1	0,3
	Injection site reaction			1	0,3
	Injection site scar	1	0,2		
	Injection site swelling	28	5,7	18	5,1
	Injection site warmth	20	4,0	10	2,8
	Lymphadenopathy	1	0,2		
	Vaccination site warmth	1	0,2		
Systemic reactions	Asthenia			1	0,3
	Body temperature fluctuation	1	0,2		
	Body temperature increased	5	1,0	4	1,1
	Chills	1	0,2		
	Crying	61	12,3	38	10,7
	Developmental delay	1	0,2		
	Fatigue	3	0,6	3	0,8
	High-pitched crying	1	0,2		
	Hyperhidrosis	1	0,2	1	0,3
	Hyperpyrexia	1	0,2	2	0,6
	Listless	4	0,8	12	3,4
	Malaise				
	Moaning	4	0,8	2	0,6
	Oedema genital	1	0,2		
	Oedema peripheral	1	0,2		
	Pain	2	0,4	1	0,3
	Peripheral swelling	2	0,4	1	0,3
	Pyrexia	73	14,8	82	23,1
	Screaming	3	0,6	1	0,3
	Swelling	1	0,2		
renal and urinary tract disorder	Chromaturia			1	0,3
	Micturition disorder	1	0,2		
	Ureteric dilatation	1	0,2		
Total		**494**	100,0	**355**	100,0

Appendix 4

Overview of reported non-serious AEFIs per SOC Vaxelis cohort (January 1, 2019 up to and including December 31, 2019) and Infanrix hexa cohort (January 1, 2018 up to and including December 31, 2018) of vaccination number 2 of the old schedule.

Systemic Organ Class (SOC)	Pt	Vaxelis N	Vaxelis %	Infanrix hexa N	Infanrix hexa %
Immune system disorders	Urticaria	2	0,6		
Metabolism and nutrition disorders	Decreased appetite	13	3,8	5	3,8
	Hypophagia	1	0,3		
Psychiatric disorders	Agitation	1	0,3		
	Anxiety	1	0,3		
	Apathy	1	0,3	1	0,8
	Breath holding	1	0,3		
	Insomnia	9	2,6	2	1,5
	Irritability	1	0,3		
	Restlessness	2	0,6		
	Sleep disorder	1	0,3		
	Somnolence	8	2,3	2	1,5
Nervous system disorders	Apparent life threatening event			1	0,8
	Depressed level of consciousness			2	1,5
	Drooling	1	0,3		
	Febrile convulsion	1	0,3		
	Headache			1	0,8
	Hypertonia	3	0,9	1	0,8
	Hypotonia	2	0,6	1	0,8
	Hypotonic-hyporesponsive episode	2	0,6		
	Infantile back arching	2	0,6		
	Loss of consciousness	1	0,3		
	Posture abnormal	1	0,3		
	Presyncope	1	0,3		
	Slow response to stimuli			2	1,5
	Syncope	2	0,6		
	Unresponsive to stimuli			1	0,8
Vascular disorders	Pallor	4	1,2	1	0,8
	Petechiae	1	0,3	5	3,8
	Purpura			1	0,8
respiratory, thoracic and mediastinal disorder	Apnoeic attack	2	0,6		
	Cough	1	0,3		
	Nasal congestion	1	0,3		
	Respiratory rate increased	1	0,3		
Gastrointestinal disorder	Abdominal pain	4	1,2	2	1,5
	Abnormal faeces	2	0,6		
	Constipation	3	0,9	2	1,5
	Diarrhoea	3	0,9		
	Discoloured vomit	1	0,3		
	Faecal volume decreased	1	0,3		
	Faeces discoloured	2	0,6		
	Flatulence	2	0,6	2	1,5
	Frequent bowel movements			1	0,8
	Regurgitation	2	0,6		
	Vomiting	8	2,3	3	2,3
Skin and subcutaneous tissue disorder	Dermatitis atopic	1	0,3		
	Eczema	1	0,3		
	Erythema	6	1,7	3	2,3
	Photosensitivity reaction	1	0,3		
	Rash	3	0,9	1	0,8
	Rash erythematous	1	0,3	2	1,5
	Rash macular	1	0,3	2	1,5
	Skin discolouration	8	2,3	1	0,8
	Skin warm	1	0,3		
Eye disorders	Eye inflammation		0,0	2	1,5
Musculoskeletal and connective tissue disorders	Muscle tightness	1	0,3		
	Musculoskeletal stiffness	1	0,3		
	Pain in extremity	2	0,6		
General disorders	Extensive swelling of vaccinated limb	3	0,9	1	0,8
	Injection site discharge			1	0,8
	Injection site erythema	19	5,5	8	6,1
	Injection site granuloma			1	0,8
	Injection site induration	3	0,9	4	3,1
	Injection site inflammation	17	5,0	4	3,1
	Injection site nodule	3	0,9	2	1,5
	Injection site pain	16	4,7	5	3,8
	Injection site rash	2	0,6	1	0,8
	Injection site swelling	27	7,9	6	4,6
	Injection site warmth	13	3,8	2	1,5
Systemic reactions	Asthenia	1	0,3		
	Body temperature decreased			2	1,5
	Body temperature increased	4	1,2	4	3,1
	Crying	49	14,3	11	8,4
	Fatigue	3	0,9	3	2,3
	Listless	7	2,0	3	2,3
	Malaise	4	1,2	1	0,8
	Moaning	2	0,6		
	Oedema genital	2	0,6		
	Pain	6	1,7	2	1,5
	Pyrexia	37	10,8	23	17,6
	Screaming	2	0,6		
ear and labyrinth disorder	Hyperacusis	1	0,3		
Total		**343**	100,0	**131**	100,0

Appendix 5

Overview of reported non-serious AEFIs per SOC Vaxelis cohort (January 1, 2019 up to and including December 31, 2019) and Infanrix hexa cohort (January 1, 2018 up to and including December 31, 2018) of vaccination number 3 of the old schedule.

		Vaxelis		Infanrix hexa	
Systemic Organ Class (SOC)	**Pt**	**N**	**%**	**N**	**%**
Metabolism and nutrition disorders	Decreased appetite	7	1,8	4	1,9
	Fluid intake reduced	2	0,5		
	Increased appetite		0,0	5	2,3
Psychiatric disorders	Agitation			1	0,5
	Apathy			1	0,5
	Hypersomnia	2	0,5	2	0,9
	Insomnia	4	1,0	2	0,9
	Restlessness	6	1,5	3	1,4
	Sleep disorder	1	0,3		
	Somnolence	15	3,8	1	0,5
	Staring		0,0	1	0,5
Nervous system disorders	Febrile convulsion	2	0,5	2	0,9
	Fontanelle bulging			2	0,9
	Hypertonia	1	0,3	2	0,9
	Hyporesponsive to stimuli	2	0,5	1	0,5
	Hypotonia	2	0,5	2	0,9
	Hypotonic-hyporesponsive episode	6	1,5	3	1,4
	Muscle twitching	1	0,3		
	Opisthotonus	2	0,5		
	Petit mal epilepsy	1	0,3		
	Syncope	2	0,5		
Vascular disorders	Pallor	2	0,5	1	0,5
	Petechiae	3	0,8	2	0,9
Cardiac disorders	Heart rate increased	1	0,3		
	Tachycardia		0,0	2	0,9
respiratory, thoracic and mediastinal disorder	Dyspnoea	11	2,8		0,0
	Nasopharyngitis	1	0,3		
	Respiratory rate increased			2	0,9
	Rhinorrhoea	2	0,5		
Gastrointestinal disorder	Abdominal pain	2	0,5		
	Constipation	2	0,5		
	Diarrhoea	5	1,3	8	3,8
	Flatulence	2	0,5		
	Frequent bowel movements			1	0,5
	Haematochezia			2	0,9
	Nausea			1	0,5
	Vomiting	16	4,0	6	2,8
Skin and subcutaneous tissue disorder	Eczema	2	0,5	2	0,9
	Erythema	2	0,5	2	0,9
	Erythema multiforme			2	0,9
	Pruritus	1	0,3		
	Rash	6	1,5		
	Rash generalised	3	0,8	1	0,5
	Rash macular			5	2,3
	Rash maculo-papular	2	0,5		
	Rash papular	5	1,3		
	Skin discolouration	7	1,8	5	2,3
	Subcutaneous haematoma	1	0,3		
Eye disorders	Eye inflammation		0,0	2	0,9
Musculoskeletal and connective tissue disorders	Pain in extremity	1	0,3	2	0,9
General disorders	Extensive swelling of vaccinated limb	3	0,8		
Injection site reactions	Injection site discolouration	4	1,0		
	Injection site erythema	23	5,8	7	3,3
	Injection site haemorrhage	3	0,8	2	0,9
	Injection site induration	2	0,5	2	0,9
	Injection site inflammation	18	4,5	7	3,3
	Injection site nodule	1	0,3	2	0,9
	Injection site pain	17	4,3	4	1,9
	Injection site rash			2	0,9
	Injection site swelling	22	5,5	10	4,7
	Injection site urticaria	1	0,3		
	Injection site warmth	16	4,0		
Systemic reactions	Body temperature decreased			1	0,5
	Body temperature increased	2	0,5	1	0,5
	Crying	52	13,1		
	Developmental delay			23	10,8
	Fatigue	6	1,5		
	Hyperpyrexia	6	1,5		
	Lip swelling	1	0,3		
	Listless	7	1,8		
	Malaise	7	1,8	3	1,4
	Moaning	2	0,5	2	0,9
	Pain	8	2,0	2	0,9
	Peripheral swelling			2	0,9
	Pyrexia	59	14,8	65	30,5
	Swelling face	2	0,5		
	Swollen tongue	1	0,3		
renal and urinary tract disorder	Micturition frequency decreased	2	0,5		
Total		**398**	100,0	**213**	100,0

Appendix 6

Overview of reported non-serious AEFIs per SOC Vaxelis cohort (January 1, 2019 up to and including December 31, 2019) and Infanrix hexa cohort (January 1, 2018 up to and including December 31, 2018) of vaccination number 4 of the old schedule.

		Vaxelis		Infanrix hexa	
Systemic Organ Class (SOC)	**Pt**	N	%	N	%
Metabolism and nutrition disorders	Decreased appetite	2	2,4	4	3,5
Psychiatric disorders	Insomnia			3	2,6
	Somnolence	2	2,4	1	0,9
Nervous system disorders	febrile convulsion			1	0,9
	Gait disturbance	1	1,2		
	Tremor	2	2,4		
respiratory, thoracic and mediastinal disorder	Cough	2	2,4		
	dyspnoea			2	1,8
	Nasopharyngitis	2	2,4		
	Productive cough	1	1,2		
Gastrointestinal disorder	Nausea	2	2,4		
	Retching	2	2,4		
	Vomiting	4	4,7	2	1,8
Skin and subcutaneous tissue disorder	rash			2	1,8
	skin discolouration			1	0,9
Musculoskeletal and connective tissue disorders	Pain in extremity	3	3,5		
General disorders	Extensive swelling of vaccinated limb	2	2,4	1	0,9
Injection site reactions	injection site abscess			3	2,6
	Injection site discolouration	2	2,4	2	1,8
	Injection site erythema	8	9,4	17	14,9
	Injection site induration	2	2,4	5	4,4
	Injection site inflammation	6	7,1	13	11,4
	Injection site pain	8	9,4	15	13,2
	injection site pruritus			2	1,8
	Injection site swelling	4	4,7	8	7,0
	Injection site warmth	8	9,4	9	7,9
Systemic reactions	Body temperature increased	1	1,2		
	Crying	4	4,7	3	2,6
	Listless	2	2,4		
	Malaise			1	0,9
	Pyrexia	15	17,6	19	16,7
Total	**Eindtotaal**	**85**	100,0	**114**	100,0

Appendix 7

Overview of reported non-serious AEFIs per SOC Vaxelis cohort (up to and including December 2019) per vaccination moment from children with the new schedule.

vaccination moment / N reports		**A / 17 reports**		**B / 4 reports**		**C / 1 report**	
Systemic Organ Class (SOC)	**Pt**	N	%	**N**	**%**	**N**	**%**
Immune system disorders	Urticaria	1	1,8				
Metabolism and nutrition disorders	Decreased appetite	2	3,6				
Psychiatric disorders	Abnormal behaviour	1	1,8				
	Somnolence	1	1,8				
Nervous system disorders	Hypertonia			2	10,0		
	Hypotonia	1	1,8				
	Hypotonic-hyporesponsive episode	2	3,6				
	Loss of consciousness	1	1,8				
Vascular disorders	Pallor	1	1,8				
respiratory, thoracic and mediastinal disorder	Cough	1	1,8				
	Dyspnoea			2	10,0		
	Nasal congestion	1	1,8				
Gastrointestinal disorder	Diarrhoea	2	3,6				
	Vomiting	2	3,6				
Skin and subcutaneous tissue disorder	Dermatitis atopic	1	1,8				
	Eczema	1	1,8	2	10,0		
	Erythema	1	1,8				
	Photosensitivity reaction	1	1,8				
	Rash			2	10,0		
	Rash papular			2	10,0		
	Skin discolouration	3	5,5				
Musculoskeletal and connective tissue disorders	Pain in extremity	1	1,8				
General disorders	Extensive swelling of vaccinated limb	1	1,8				
Injection site reactions	Injection site erythema	3	5,5			2	25,0
	Injection site induration	1	1,8	2	10,0		
	Injection site inflammation	2	3,6			2	25,0
	Injection site pain	3	5,5			2	25,0
	Injection site swelling	3	5,5				
	Injection site warmth	2	3,6				
Systemic reactions	Body temperature increased	1	1,8	1	5,0	2	25,0
	Crying	9	16,4	3	15,0		
	Oedema genital	1	1,8				
	Pyrexia	5	9,1	4	20,0		
Total		**55**	100,0	**20**	100,0	**8**	100,0