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

Introduction

At the end of 2018 the diphtheria-pertussis-tetanus-IPV-HiB-hepB vaccine Infanrix hexa® was replaced by Vaxelis® in the National Immunization Program of the Netherlands (RVP). Vaxelis® has been licensed since February 15, 2016 [1]. As standard in the current legislation it is drug under additional monitoring which implies that amongst others, 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 diphtheria-tetanus-acellulair pertussis vaccine (dTap), was introduced in the RVP [3]. For infants of mothers who were vaccinated with dTap during pregnancy, the vaccination schedule is modified (table 1). 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 and/or preterm infants 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 events 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?

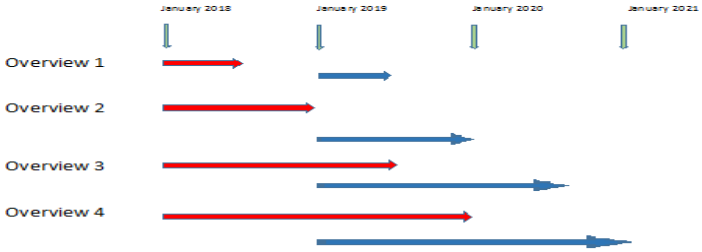

Figure 1 Comparable reporting periods in time for the overviews. Red arrows represent the Infanrix hexa cohort and the blue arrows the Vaxelis cohort.

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 two overviews have been already published [4,5]. Overview 3 will be presented in the present report and 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). This overview will be published in 2021.

The two cohorts and the comparison of these cohorts are followed under the provisional assumption that both cohorts are about 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 this third overview spontaneous reports were selected after administration of Vaxelis® from children born between December 1, 2018 and July 1, 2020, which were received in the period from January, 1 2019 to July 1, 2020 (Vaxelis cohort) and spontaneous serious and non-serious reports and reported serious and non-serious AEFIs of Infanrix hexa® from children born between December 1, 2017 and July 1, 2019, which were received in the period from January, 1 2018 to July 1, 2019 (Infanrix hexa cohort).

Table 2. Overview of the number of spontaneous serious and non-serious reports and reported serious and non-serious AEFIs of Vaxelis® from children born between December 1, 2018 and July 1, 2020, which were received in the period from January, 1 2019 to July 1, 2020 (Vaxelis cohort) and spontaneous serious and non-serious reports and reported serious and non-serious AEFIs of Infanrix hexa® from children born between December 1, 2017 and July 1, 2019, which were received in the period from January, 1 2018 to July 1, 2019 (Infanrix hexa cohort).

Vaccination schedule*	Infanrix hexa						Vaxelis cohort					
	Number non-serious reports	Number serious reports	Total number reports	Number non-serious AEFIs	Number serious AEFIs	Total number AEFIs	Number non-serious reports	Number serious reports	Total number reports	Number non-serious AEFIs	Number serious AEFIs	Total number AEFIs
8 weeks (1)	160(89.9%)	18 (10.1%)	178 (100%)	398 (89.4%)	47 (10.6%)	445 (100%)	204 (91.9%)	18 (8.1%)	222 (100%)	647 (91.4%)	61 (8.6%)	708 (100%)
12 weeks (2)	63 (88.7%)	8 (11.3%)	71 (100%)	152 (89.9%)	17 (10.1%)	169 (100%)	87 (93.5%)	6 (6.5%)	93 (100%)	289 (93.2%)	21 (6,8%)	310 (100%)
12 weeks (A)							82 (96.5%)	3 (3.5%)	85 (100%)	226 (96.2%)	9 (3.8%)	235 (100%)
16 weeks (3)	95 (92.2%)	8 (7.8%)	103 (100%)	231 (87.5%)	33 (12.5%)	264 (100%)	79 (88.8%)	10 (11.2%)	89 (100%)	229 (91.2%)	22 (8.8%)	251 (100%)
20 weeks (B)							38 (95.0%)	2 (5.0%)	40 (100%)	97 (95.1%)	5 (4.9%)	102 (100%)
11 months (4/C)	125 (96.2%)	5 (3.8%)	130 (100%)	450 (94.5%)	26 (5.5%)	476 (100%)	104 (99.0%)	1 (1.0%)	105 (100%)	366 (99.7%)	1 (0.3%)	367 (100%)
Total	443 (91.9%)	39 (8.1%)	482 (100%)	1,231 (90.9%)	123 (9.1%)	1,354 (100%)	594 (93.7%)	40 (6.3%)	634 (100%)	1,854 (94.0%)	119 (6.0%)	1,973 (100%)

* The numbers 1 to 4 of the vaccination schedule corresponds with the vaccination numbers 1 to 4 of the old classical schedule (schedule 3+1) and the letters A to C with the vaccination moments in the new schedule after maternal pertussis prophylaxis (schedule 2+1).

Table 2 provides an overview of the number of serious and non-serious reports and the number of reported serious and non-serious AFEIs from the Vaxelis® and Infanrix hexa® cohort. From the Vaxelis cohort 634 reports have been

received. Of these reports, the brand name of the vaccine was confirmed in 550 reports by means of the batch number (86.8%). In the Infanrix hexa® cohort 482 reports have been received in the comparable period one year earlier of which 404 confirmed cases based on the batch number (83.8%). The difference in number of reports between the Vaxelis® cohort and Infanrix hexa® cohort was 31.5%. Based on our current data, more reports were received in the Vaxelis® cohort during the priming phase compared to the Infanrix hexa cohort (529 versus 352 reports). After the first booster vaccination, the difference appears to be reversed and more reports were received in the infanrix hexa cohort compared to the Vaxelis cohort (130 versus 105 reports).

A report may contain multiple AEFIs. The total number of reported AEFIs in the Vaxelis® cohort is 1,973 out of 634 reports (3.1 AEFIs per report) compared to 1,354 AEFIs out of 482 reports (2.8 AEFIs per report) in the Infanrix hexa® cohort, an increase of 45.7%.

Serious reports and reported AEFIs
Table 2 shows the number of serious and non-serious reports per vaccination number of the series. Following the Council for International Organizations of Medical Sciences criteria (CIOMS criteria) for seriousness, 6.3% of the Vaxelis® cohort are serious and 8.1% of the Infanrix hexa® cohort. In the Vaxelis® cohort as well in the Infanrix hexa® cohort most serious reports were reported during the priming phase and less after the first booster vaccination at the age of 11 months

Serious reports of death
In the first 12 months of monitoring were three reports with fatal outcome reported in the Vaxelis® cohort and one report with fatal outcome in the Infanrix hexa® cohort. These cases has been described in overview 1 and 2. In the follow-up period 12 – 18 months there have been no new reports with fatal outcome reported in the Vaxelis® cohort and in the Infanrix hexa cohort.

Other serious reports without reports of death
The other 37 serious reports in the Vaxelis® cohort concerned reports of hospital admissions (34x), life threatening events (3x) and serious other medically important condition (4x). Sixteen of these events occurred after the first vaccination, six after the second and nine after the third vaccination.
The number of serious reports of children whose mothers were vaccinated during pregnancy (maternal pertussis vaccination) are limited: 3 after the first vaccination and 2 after the second vaccination. One serious report occurred after the first booster at the age of eleven months (see table 2). These 37 serious reports contains in total 116 AEFIs (3.1 AEFI per report).
The other 38 serious reports in the Infanrix hexa® cohort concerned reports of hospital admission (34x) and reports of life threatening (6x). Eighteen of these events occurred after the first vaccination and eight as well after the second as after the third vaccination and four after the first booster at the age of eleven months. These 38 serious reports contains in total 121 AEFIs (3.1 AEFIs per report).

Appendix 2 provides an overview of reported serious AEFIs (coded MedDRA PT) per SOC without AEFIs of reports with fatal outcome. The type of serious adverse events reported between the Vaxelis® cohort and Infanrix hexa® cohort is similar and are well-known AEFIs.
Many hospital admissions in the Vaxelis® cohort as well as in the Infanrix hexa® cohort were related to short-lasting events known as Hypotonic Hyporesponsive Event (HHE[1]), Apparent Life Threatening Event (ALTE) and syncope. Infants with an HHE /ALTE /syncope are often admitted to the hospital for 24-hour monitoring. Further investigations and monitoring show generally no abnormalities as was the case in the cases reported.
There were some serious reports of non-febrile and febrile convulsions in both the Vaxelis cohort and in the Infanrix hexa cohort. These rare AEFIs are known events from post-marketing surveillance.
Both in the Vaxelis cohort as in the Infanrix hexa cohort there were a few serious reports of hospital admissions related to apnea and dyspnea.
Most serious AEFIs were reported incidentally. Appendix 3 provides a detailed description of all serious reports.

Non-serious AEFIs
Appendix 4 provides an overview of all reported non-serious AEFIs (coded PT) per System Organ Class (SOC) per cohort. In the Vaxelis® cohort, 1,854 non-serious AEFIs were reported out of 594 non-serious reports (3.1 AEFIs per report) in the period January 1, 2019 until June 30, 2020. The Infanrix hexa cohort included 1,231 non-serious

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

AEFIs out of 443 non-serious reports (2.8 AEFI per report), reported in the comparable period one year earlier (January 1, 2018 until June 30, 2019).

The number of reports and the number of AEFIs differs per vaccination moment at infant age. The vast majority are reported after administration of the first vaccination at the age of two months. The type of reported AEFIs also differ per vaccination moment. For this reason, AEFIs are broken down by vaccination moment. Appendix 4 up to 6 provides an overview of the reported AEFIs per vaccination moment of the old schedule. Appendix 7 provides an overview of AEFIs after the first booster vaccination at the age of 11 months (vaccination number 4 old schedule and C new schedule).

AEFIs after the first vaccination (Appendix 5)
After the first administration 647 non-serious AEFIs out of 204 reports have been reported in the Vaxelis® cohort (3.2 AEFI per report) against 398 AEFIs out of 160 reports in the Infanrix hexa®cohort (2.5 AEFI per report).
Notable is the difference in the number of reported injection site reactions (Vaxelis® cohort 186x versus Infanrix hexa® cohort 93x). It concerns in particular an increase 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 57 reports (27.9%) with one or more injection site reactions compared to 33 reports of one or more injection site reactions in the Infanrix hexa® cohort (20.6%). Of these 57 reports in the Vaxelis® cohort, it concerned six reports of ELS compared to zero reports of ELS in the Infanrix hexa® cohort.
Also crying, including screaming and high pitch crying, has been more frequently reported after administration of Vaxelis® / Synflorix® (n=90) compared to Infanrix hexa® / Synflorix® (n=50). As well in the Vaxelis® cohort as in Infanrix hexa®cohort pyrexia (pyrexia / hyperpyrexia / increased body temperature) have been frequently reported (n=297 versus n=256).

AEFIs after the second vaccination (Appendix 6)
After the second administration 289 non-serious AEFIs out of 87 reports have been reported in the Vaxelis® cohort (3.3 AEFI per report) against 152 AEFIs out of 63 reports in the Infanrix hexa cohort (2.4 AEFI per report).
There is slight difference in the number of reported injection site reactions (Vaxelis® cohort 81x versus Infanrix hexa® cohort 63x). In the Vaxelis® cohort there are 23 reports (26.4%) with one or more injection site reactions compared to 20 reports with one or more injection site reactions in the Infanrix hexa® cohort (31.7%). Of these 23 reports in the Vaxelis® cohort, it concerned one report of ELS compared to two reports of ELS out 20 reports in the Infanrix hexa® cohort.
Also crying, including screaming and high pitch crying, has been more frequently reported in the Vaxelis® cohort (n=35) compared to the Infanrix hexa® cohort (n=8). Other notable differences between the Vaxelis cohort and the Infanrix hexa® cohort are the number of reports of pyrexia / hyperpyrexia / increased body temperature (38x versus 26x) and gastrointestinal complaints (29x versus 12x).

AEFIs after the third vaccination (Appendix 7)
After the 3rd administration 229 non-serious AEFIs out of 79 reports have been reported in the Vaxelis® cohort (2.9 AEFI per report) against 231 AEFIs out of 95 reports in the Infanrix hexa cohort (2.4 AEFI per report).
There is a slight difference in the number of reported injection site reactions (Vaxelis® cohort 43x versus Infanrix hexa® cohort 58x). In the Vaxelis® cohort there are 15 reports (20.0%) with one or more injection site reactions compared to 21 reports with one or more injection site reactions in the Infanrix hexa® cohort (22.1%). Of these 15 reports in the Vaxelis® cohort, it concerned one report of ELS compared to one report of ELS out 21 reports in the Infanrix hexa® cohort.
Crying, including screaming has been more frequently reported AEFIs in the Vaxelis® cohort (n=33) compared to the Infanrix hexa® cohort (n=17). Pyrexia /hyperpyrexia /increased body temperature has been more frequently reported In the Infanrix hexa® cohort (61x) compared to the Vaxelis® cohort (36x).

AEFIs after the first booster vaccination (age 11 months; vaccination number 4 of the old schedule / C of the new schedule (Appendix 8)
After the 4th administration 366 non-serious AEFIs out of 104 reports have been reported in the Vaxelis® cohort (3.5 AEFI per report) against 450 AEFIs out of 125 reports in the Infanrix hexa® cohort (3.6 AEFI per report).
Notable is the difference in the number of reported injection site reactions (Vaxelis® cohort 149x versus Infanrix hexa® cohort 257x). In the Vaxelis® cohort there are 44 reports (42.3%) with one or more injection site reactions compared to 65 reports with one or more injection site reactions in the Infanrix hexa cohort (52.0%). Of these 44 reports in the Vaxelis® cohort, it concerned four reports of ELS compared to five reports of ELS out 65 reports in the Infanrix hexa® cohort.

Pyrexia /hyperpyrexia /increased body temperature has been more frequently reported In the Infanrix hexa cohort (75x) compared to the Vaxelis® cohort (51x).

Appendix 9 provides an overview of the reported AEFIs of children who are vaccinated according to the new vaccination schedule at the age of 3 months and 5 months. As these children follow a new vaccination schedule, the reports and reported AEFIs are difficult to compare with the Infanrix hexa cohort.

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® [6].

Discussion and conclusion

This report is the third overview of a total of four semi-annual reports in which the first birth cohort children that are vaccinated with Vaxelis® will be compared to the last birth cohort 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 - June 30, 2020 Pharmacovigilance Center Lareb received 31.5% 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 - June 30, 2019). In the Vaxelis cohort, 45.7% more AEFIs were reported compared to the Infanrix hexa cohort.

In the Vaxelis® cohort 40 reports out of 634 reports (6.3%) were serious and in the Infanrix hexa® 39 out of 482 (8.1%). In comparison to the first and second overview the relative number of serious reports in the Vaxelis® cohort has decreased from 8.8% and 7.1% to 6,3%. The relative number of serious reports in the Infanrix hexa® cohort decreased from 10% (first overview) and 9.4% (second overview) to 8.1%. This decrease in both cohorts can be explained by the fact that serious reports are relatively more often reported after the first vaccinations. The first overview almost exclusively related to reports of the first vaccinations.
In both cohorts, most serious reports were reported after priming vaccine administrations, mainly hospital admissions related to short-lasting events of pallor, hypotonia, and hyporesponsivity. These events are known as Hypotonic Hyporesponsive Event (HHE).

More non-serious reports were reported in the Vaxelis® cohort than in the Infanrix hexa® cohort (594 versus 443) and more non-serious AEFIs were reported (1854 versus 1231). The majority of these non-serious AEFIs are well known AEFIs. Many reports relate to injection site reactions. The number of reports of injection site reactions in the Vaxelis® cohort during the priming phase is higher than the number in the Infanrix hexa® cohort. After the first booster administration at 11 months of age, this difference appears to be reversed and more injection site reactions appear to be reported in the Infanrix hexa cohort. Crying is also reported more frequently in the Vaxelis® cohort compared to the Infanrix hexa® cohort during the priming phase.

The third 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://www.rivm.nl/sites/default/files/2018-11/20110907%20Q%26A%20Uitbreiding%20Rijksvaccinatieprogramma%20met%20hepatitis%20B.pdf
3. https://rijksvaccinatieprogramma.nl/over-het-programma
4. https://databankws.lareb.nl/Downloads/Signals_2019_overview%20AEFIs%20Vaxelis%20compared%20Infanrix%20hexa.pdf
5. https://databankws.lareb.nl/Downloads/Signals_2020_reported_AEFIs_Vaxelis_compared_Infanrix_hexa_second_overview.pdf
6. 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 February 10, 2021. 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

Overzicht van bijwerkingen in tabelvorm

Voor de classificatie van de bijwerkingen is de volgende conventie gebruikt:
Zeer vaak (≥ 1/10)
Vaak (≥ 1/100, < 1/10)
Soms (≥ 1/1000, < 1/100)
Zelden (≥ 1/10.000, < 1/1000)
Zeer zelden (< 1/10.000)
Niet bekend (kan met de beschikbare gegevens niet worden bepaald)

Tabel 1: Lijst met bijwerkingen

MedDRA 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
Maag-darmstelselaandoeningen	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	Blauwe plek op de injectieplaats, induratie op de injectieplaats, nodule op de injectieplaats
	Soms	Huiduitslag op de injectieplaats, warmte op de injectieplaats, vermoeidheid

Postmarketing-surveillance
De volgende bijwerkingen zijn gemeld tijdens postmarketinggebruik. Omdat deze bijwerkingen gemeld werden vanuit een populatie van onbekende grootte, is het over het algemeen niet mogelijk om de frequentie van deze bijwerkingen op betrouwbare wijze te schatten of om een causaal verband met het vaccin vast te stellen.

MedDRA Systeem/orgaanklasse	Frequentie	Bijwerkingen
Zenuwstelselaandoeningen	Niet bekend	Hypotone-hyporesponsieve episode (HHE)(zie rubriek 4.4)

Beschrijving van 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 van 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, gevoeligheid 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.

Premature zuigelingen

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

Appendix 2

Overview of reported serious AEFIs per SOC without AEFIs of reports serious death. Vaxelis cohort (January 1, 2019 up to and including June 30, 2020) and Infanrix hexa cohort (January 1, 2018 up to and including June 30, 2019).`

		Vaxelis	Infanrix hexa
	Number of serious cases without death reports	N=37 cases	N=38 cases
System Organ Class (SOC)	Preferred term (Pt)	Number AEFIs	number AEFIs
Blood and lymphatic system disorders	Immune thrombocytopenia		1
	Leukopenia		1
Cardiac disorders	Bradycardia		1
	Cyanosis	4	3
	Tachycardia	2	1
Eye disorders	Eye movement disorder	1	1
Gastrointestinal disorders	Abdominal pain	1	
	Abnormal faeces	1	
	Aphthous ulcer		1
	Constipation	1	
	Diarrhoea		1
	Gastrointestinal pain	1	
	Gastrooesophageal reflux disease		1
	Haematochezia	1	
	Nausea	2	
	Necrotising colitis	1	
	Retching	1	
	Vomiting	6	3
General disorders and administration site	Condition aggravated	1	
	Crying	7	3
	Extensive swelling of vaccinated limb		1
	Fatigue		1
	Hyperpyrexia		1
	Injection site erythema		1
	Injection site inflammation	1	
	Injection site pain	2	
	Injection site swelling	1	2
	Injection site warmth	1	1
	Malaise	1	1
	Moaning	1	1
	Pain	1	
	Peripheral swelling		1
	Pyrexia	12	16
Infections and infestations	Injection site abscess		1
	Nasopharyngitis	**1**	
	Pneumonia viral		1
	Pyelitis	1	
	Urinary tract infection	1	
Investigations	Body temperature decreased		1
	Body temperature increased		2
	C-reactive protein increased	1	
	Oxygen saturation decreased		2
Metabolism and nutrition disorders	Decreased appetite	**2**	1
	Dehydration		2
	Hypertriglyceridaemia	1	
	Hypophagia	1	2
	Increased appetite	1	
	fat intolerance	1	
Nervous system disorders	Apparent life threatening event	3	4
	Cerebral haemorrhage		1
	Convulsions local		1
	Epilepsy	1	
	Febrile convulsion	6	1
	Hypertonia	1	1
	Hyporesponsive to stimuli	3	4
	Hypotonia	4	5
	Hypotonic-hyporesponsive episode	7	9
	Infantile spasms		1
	Loss of consciousness		2
	Seizure	2	3
	Somnolence	2	5
	Syncope	1	5
	Tremor	1	
	Unresponsive to stimuli	2	
Psychiatric disorders	Apathy		1
	Breath holding	1	
	Insomnia		1
	listless	1	
Renal and urinary disorders	Micturition disorder	1	
	Ureteric dilatation	1	
Respiratory, thoracic and mediastinal	Apnoea	3	1
	Apnoeic attack		1
	Choking	1	1
	Cough		2
	Dyspnoea	2	4
	Increased upper airway secretion		1
Skin and subcutaneous tissue disorders	Acute haemorrhagic oedema of infancy	1	

	Ecchymosis	1	
	Hyperhidrosis	1	1
	Petechiae	2	1
	Rash		1
	Rash papular		1
Vascular disorders	Pallor	6	6
	Peripheral coldness		**1**
	Total	**116**	**121**

Appendix 3

Detailled description of serious reports without serious reports with fatal outcome. Vaxelis cohort (January 1, 2019 up to and including June 30, 2020) and Infanrix hexa cohort (January 1, 2018 up to and including June 30, 2019).

Many 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). In the Vaxelis cohort it concerned 7 cases and in the Infanrix hexa cohort 11 cases. These short-lasting events were sometimes reported or coded by the assessor of Lareb as an apparent life threatening event (ALTE; Vaxelis cohort 3x; Infanrix hexa cohort 4x) or as syncope (Vaxelis cohort 1x; Infanrix hexa cohort 2x). Infants with an HHE /ALTE /Syncope are often admitted to the hospital for 24-hour monitoring. Further investigations and monitoring show generally no abnormalities such as in the cases reported. Some children with HHE were not admitted to the hospital. These serious reports were qualified as serious life threatening or as serious other medically important condition. In addition there were also reports of HHE received and coded as non-serious events.
In the Vaxelis cohort 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.

In the Vaxelis cohort 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 administration of a 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.
In the Infanrix hexa cohort five hospital admissions related to suspicion of a convulsion. One time it concerned an infant with focal convulsion 5 hours after the third vaccination. The child had also a convulsion after the second administration. 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. The fourth hospital admission concerned an afebrile convulsion, with apathy, somnolence and fatigue after the third vaccination. The fifth report concerned of infantile spasms after the third vaccination. The MRI showed a cerebral infarction, probably emerged in the first half of the pregnancy. The diagnosis cerebral palsy was made, but a possible relation with epilepsy / West Syndrome is not clear.

In the Vaxelis cohort, 5 hospitalizations were reported for febrile convulsion. In addition, one febrile convulsion was reported without hospitalization (serious other medically important condition). In the Infanrix hexa cohort, one hospitalization was reported for febrile convulsion.

In the Vaxelis cohort there were three serious reports of apnea (hospitalization 2x; serious other 1x). One of these reports concerned a report of recurrent 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. In the Infanrix hexa cohort there were two reports of hospital admission for apnea.
In the Vaxelis cohort there was one report of hospital admission for dyspnea and one for choking. In the Infanrix hexa there were four reports of hospital admissions for dyspnea and one report of hospital admission for choking. Two times it concerned choking / breathing difficulties with excessive salivation after vaccination.

A number of reports related to hospitalizations associated with pyrexia. In the Vaxelis cohort it concerned five report. Two times it concerned pyrexia in combination with an urinary tract infection. One report concerned a hospital admission 6 days after the second vaccination due to pyrexia and nasopharyngitis (child with a medical history of a congenital heart defect). One report concerned a brief hospital admission due to pyrexia and increased CRP. One brief hospital admission one day after the vaccination concerned pyrexia and somnolence during the COVID-19 epidemic (COVID-19 infection was excluded). In the Infanrix hexa cohort it concerned 3 reports. One report, was a report of hyperpyrexia, dehydration and viral pneumonia. There was a report of pyrexia, leukopenia and aphthae. The third report was a report of peripheral swelling, pyrexia and rash ten hours after the first administration.

There were three reports of petechiae. In the Vaxelis cohort it concerned two reports. One child of 5 months old was hospitalized for observation due to petechiae 4 hours after the vaccination. The other report concerned a child of 7 months old, which was hospitalized due to acute haemorrhagic oedema of infancy (AHOI) on the legs and petechiae after the third administration of Vaxelis® and Synflorix®. The child had also an AHOI reaction after the second administration of Vavelis®. In the Infanrix hexa cohort one child was admitted to the hospital for idiopathic thrombocytopenic purpura (ITP) with petechiae three days after the second vaccination. Viral infections were excluded.

In the Vaxelis cohort one serious report concerned a premature born infant (gestational age 27 weeks) with a hospital admission for a necrotizing enterocolitis after the 1st administration of Vaxelis®, Synflorix® and rotavirus-vaccine at the age of 9 weeks.
In the Vaxelis cohort one serious other medically important condition concerned a report of a child 13 months old known with fat intolerance with an temporally aggravation of the symptoms after the first administration of Vaxelis® and Synflorix®.

In the Infanrix hexa cohort there were two reports of hospital admissions of severe local reactions. One report concerned an injection site abscess (culture: streptococcus haemolyticus group A) eleven days after the vaccination. The other report concerned an extensive swelling of the vaccinated limb after the third vaccination.
In the Infanrix hexa cohort one infant was admitted to the hospital due to persistent gastroesophageal reflux developed 4 to 5 days after the first vaccinations.

Appendix 4

Overview of all reported non-serious AEFIs per SOC Vaxelis cohort (January 1, 2019 up to and including June 30, 2020) and Infanrix hexa cohort (January 1, 2018 up to and including June 30, 2019).`

		Vaxelis	Infanrix hexa
	Number of serious cases	N= 594 Reports	N= 443 Reports
System Organ Class (SOC)	Preferred term (Pt)	number AEFIs	number AEFIs
Blood and lymphatic system disorders	Anaemia	1	
	Lymphadenopathy	1	
Cardiac disorders	Cyanosis	4	3
Ear and labyrinth disorders	Ear swelling	1	
	Hyperacusis	1	
Eye disorders	Eye inflammation		3
	Eye movement disorder	3	1
	Eye swelling	2	
	Gaze palsy	2	
	Strabismus	1	1
	Swelling of eyelid		1
Gastrointestinal disorders	Abdominal pain	11	4
	Abnormal faeces	1	2
	Constipation	7	3
	Diarrhoea	21	13
	Discoloured vomit	1	
	Faeces discoloured	5	
	Flatulence	5	4
	Frequent bowel movements	3	2
	Gastrointestinal pain	4	2
	Gastrooesophageal reflux disease	4	
	Haematochezia	1	1
	Infrequent bowel movements	1	
	Lip swelling	1	
	Nausea	4	1
	Regurgitation	2	
	Retching	1	2
	Salivary hypersecretion	1	
	Swollen tongue	1	
	Vomiting	60	29
	Vomiting projectile	2	1
General disorders and administration site conditions	Administration site induration		1
local reactions	Extensive swelling of vaccinated limb	14	8
	Injected limb mobility decreased	1	
	Injection site bruising	1	2
	Injection site discharge	1	2
	Injection site discolouration	4	8
	Injection site discomfort	3	1
	Injection site erythema	108	96
	Injection site granuloma		1
	Injection site haematoma	4	4
	Injection site haemorrhage	2	1
	Injection site induration	9	22
	Injection site inflammation	96	89
	Injection site mass		1
	Injection site nodule	5	6
	Injection site pain	83	63
	Injection site papule		1
	Injection site pruritus	2	7
	Injection site rash	5	2
	Injection site reaction		2
	Injection site scar	1	
	Injection site swelling	116	93
	Injection site urticaria	1	
	Injection site vesicles		1
	Injection site warmth	62	60
	Vaccination site warmth	1	
General disorders and administration site conditions	Asthenia	2	1
systemic reactions	Chills	3	1
	Condition aggravated	1	
	Crying	214	93
	Decreased activity	1	
	Developmental delay	1	
	Fatigue	18	9
	Feeling jittery		2
	Gait disturbance	2	
	General physical health deterioration	1	
	High-pitched crying	2	
	Hyperpyrexia	8	6
	Malaise	11	4
	Moaning	10	2
	Oedema peripheral	4	
	Pain	17	4
	Peripheral swelling	5	3
	Pyrexia	264	239
	Screaming	17	2
	Swelling	2	1
	Swelling face	2	
	Thirst decreased	1	1

Immune system disorders	Food allergy	1	
Infections and infestations	Ear infection	2	1
	Erythema infectiosum		1
	Exanthema subitum		1
	Gastrointestinal viral infection		1
	Gianotti-Crosti syndrome		1
	Gingivitis		1
	Injection site abscess	1	1
	Injection site infection		1
	Injection site pustule		1
	Nasopharyngitis	5	3
	Respiratory tract infection	1	
	Subglottic laryngitis		1
	Urinary tract infection		1
Injury, poisoning and procedural complications	Fall		1
	Incorrect route of product administration		1
	Subcutaneous haematoma	1	
	Vaccination error	1	
Investigations	Body temperature decreased	2	3
	Body temperature fluctuation	3	
	Body temperature increased	25	11
	Cardiac murmur		1
	Faecal volume decreased	1	
	Heart rate increased	1	
	Respiratory rate decreased	1	
	Respiratory rate increased	1	1
Metabolism and nutrition disorders	Decreased appetite	49	22
	Fluid intake reduced	2	
	Hypophagia	5	1
	Increased appetite	1	4
	Poor feeding infant		2
	Weight gain poor	1	
Musculoskeletal and connective tissue disorders	Arthritis	1	
	Infantile back arching	2	
	Limb discomfort	1	
	Mobility decreased	1	
	Muscle spasms		1
	Musculoskeletal stiffness		2
	Muscle tightness	1	
	Muscle twitching	2	
	Muscular weakness	2	
	Musculoskeletal stiffness	2	
	Myalgia	1	
	Neck deformity	1	
	Pain in extremity	16	6
	Posture abnormal	1	1
Nervous system disorders	Apparent life threatening event		1
	Depressed level of consciousness	2	3
	Dizziness		1
	Drooling	1	
	Dyskinesia	1	1
	Exaggerated startle response	1	
	Febrile convulsion	7	9
	Fontanelle bulging		1
	Head titubation	1	
	Headache	2	5
	Hypersomnia	5	2
	Hypertonia	6	2
	Hyporesponsive to stimuli	8	5
	Hypotonia	12	7
	Hypotonic-hyporesponsive episode	13	11
	Loss of consciousness	2	
	Myoclonus	1	3
	Opisthotonus	1	
	Petit mal epilepsy	1	
	Poor quality sleep	4	2
	Poor sucking reflex	1	
	Presyncope	1	
	Psychomotor hyperactivity	1	
	Seizure	2	2
	Slow response to stimuli	2	1
	Somnolence	47	23
	Syncope	7	1
	Tremor	2	
	Unresponsive to stimuli	2	2
Psychiatric disorders	Aberrant motor behaviour	1	
	Abnormal behaviour	8	
	Abnormal dreams	1	
	Agitation	2	1
	Anxiety	3	
	Apathy	3	5
	Behaviour disorder	1	1
	Breath holding	4	1
	Conversion disorder	1	
	Delirium febrile	1	
	Insomnia	25	11

	Irritability	5	1
	Listless	32	24
	Mood altered	1	
	Nervousness		1
	Nightmare		1
	Panic reaction	2	
	Restlessness	21	5
	Sleep disorder	5	2
	Staring	3	1
	Trichotillomania	1	
Renal and urinary disorders	Anuria	1	
	Chromaturia		1
	Micturition frequency decreased	2	
Reproductive system and breast disorders	Oedema genital	1	
Respiratory, thoracic and mediastinal disorders	Apnoea	3	1
	Apnoeic attack	1	
	Asthma		1
	Catarrh		1
	Choking	2	
	Cough	5	1
	Dysphonia	1	
	Dyspnoea	11	3
	Irregular breathing	1	2
	Nasal congestion	1	
	Oropharyngeal pain		1
	Productive cough	2	
	Respiration abnormal	5	1
	Respiratory disorder	1	
	Rhinorrhoea	4	
	Tachypnoea		1
	Wheezing		1
Skin and subcutaneous tissue disorders	Angioedema		1
	Cold sweat		1
	Dermatitis atopic	1	
	Eczema	8	2
	Erythema	11	8
	Erythema multiforme		1
	Hyperhidrosis	3	1
	Livedo reticularis	3	1
	Nail discolouration	1	
	Nodular rash		1
	Petechiae	10	8
	Photosensitivity reaction	1	
	Pruritus	4	
	Purpura	2	1
	Rash	15	19
	Rash erythematous	7	7
	Rash macular	7	7
	Rash maculo-papular	2	
	Rash papular	7	2
	Rash pruritic	2	1
	Rash vesicular	1	
	Skin discolouration	34	14
	Skin warm	1	
	Urticaria	10	5
	Yellow skin	2	
Vascular disorders	Pallor	32	16
	Peripheral coldness	3	1
	Vasodilatation	1	1
	Total	**1854**	**1231**

Aappendix 5

Overview of reported non-serious AEFIs per SOC Vaxelis cohort (January 1, 2019 up to and including June 30, 2020) and Infanrix hexa cohort (January 1, 2018 up to and including June 30, 2019) of vaccination number 1 of the old schedule

		Vaxelis	Infanrix hexa
	Number of serious cases	N= 204 Reports	N= 160 Reports
System Organ Class (SOC)	Preferred term (Pt)	number AEFIs	number AEFIs
Blood and lymphatic system disorders	Anaemia	1	
	Lymphadenopathy	1	
Cardiac disorders	Cyanosis	2	1
Eye disorders	Eye movement disorder	1	
	Strabismus	1	1
Gastrointestinal disorders	Abdominal pain	**4**	2
	Abnormal faeces	1	2
	Constipation	2	1
	Diarrhoea	5	4
	Faeces discoloured	3	
	Flatulence	**1**	2
	Frequent bowel movements		1
	Gastrointestinal pain	2	2
	Gastrooesophageal reflux disease	3	
	Haematochezia	1	
	Nausea	1	
	Regurgitation	1	
	Retching		1
	Salivary hypersecretion	1	
	Vomiting	12	10
	Vomiting projectile	2	1
General disorders and administration site conditions	Extensive swelling of vaccinated limb	6	
local reactions	Injection site bruising	1	
	Injection site discharge	1	1
	Injection site discolouration		3
	Injection site erythema	35	15
	Injection site haematoma	2	1
	Injection site haemorrhage	1	
	Injection site induration	3	8
	Injection site inflammation	33	19
	Injection site nodule		1
	Injection site pain	36	13
	Injection site pruritus		1
	Injection site reaction		1
	Injection site scar	1	
	Injection site swelling	42	20
	Injection site warmth	24	10
	Vaccination site warmth	1	
General disorders and administration site conditions	Asthenia		1
systemic reactions	Chills	2	
	Crying	81	49
	Developmental delay	1	
	Fatigue	3	5
	Feeling jittery		2
	High-pitched crying	1	
	Hyperpyrexia	3	2
	Malaise	1	
	Moaning	6	2
	Oedema peripheral	2	
	Pain	4	1
	Peripheral swelling	1	2
	Pyrexia	93	89
	Screaming	8	1
	Swelling	1	
	Thirst decreased		1
Infections and infestations	Ear infection	1	
	Exanthema subitum		1
	Gingivitis		1
	Nasopharyngitis		1
Injury, poisoning and procedural complications	Incorrect route of product administration		1
	Vaccination error	1	
Investigations	Body temperature fluctuation	1	
	Body temperature increased	7	3
	Cardiac murmur		1
	Heart rate increased	1	
	Respiratory rate decreased	1	
	Respiratory rate increased	1	
Metabolism and nutrition disorders	Decreased appetite	17	7
	Hypophagia	4	1
	Increased appetite		1
	Poor feeding infant		2
	Weight gain poor	1	

Musculoskeletal and connective tissue disorders	Muscle tightness	1	
	Musculoskeletal stiffness	2	1
	Pain in extremity	4	3
	Posture abnormal		1
Nervous system disorders	Depressed level of consciousness	1	2
	Dyskinesia	1	1
	Exaggerated startle response	1	
	Febrile convulsion	1	1
	Headache		1
	Head titubation	1	
	Hypersomnia	3	1
	Hypertonia		1
	Hyporesponsive to stimuli	4	3
	Hypotonia	7	4
	Hypotonic-hyporesponsive episode	7	7
	Loss of consciousness	1	
	Myoclonus		1
	Poor quality sleep	1	
	Poor sucking reflex	1	
	Presyncope	1	
	Seizure	1	
	Slow response to stimuli	**1**	
	Somnolence	**20**	19
	Syncope	2	1
	Tremor	1	
	Unresponsive to stimuli	2	1
Psychiatric disorders	Aberrant motor behaviour	1	
	Abnormal behaviour	2	
	Agitation	1	1
	Anxiety	3	
	Behaviour disorder	1	
	Breath holding	3	1
	Insomnia	6	3
	Irritability	3	1
	Listless	6	13
	Mood altered	1	
	Nervousness		1
	Panic reaction	1	
	Restlessness	6	1
	Sleep disorder	2	
	Staring	2	
Renal and urinary disorders	Chromaturia		**1**
Reproductive system and breast disorders	Oedema genital	1	
Respiratory, thoracic and mediastinal disorders	Apnoea	2	1
	Catarrh		1
	Choking	1	
	Cough	2	
	Dysphonia	1	
	Dyspnoea	4	
	Respiration abnormal	3	
	Respiratory disorder	1	
Skin and subcutaneous tissue disorders	Eczema	2	
	Erythema	3	2
	Hyperhidrosis	1	1
	Livedo reticularis	2	
	Nodular rash		1
	Petechiae	4	3
	Rash	4	4
	Rash erythematous	3	1
	Rash macular	1	1
	Rash maculo-papular	1	
	Rash papular	1	1
	Rash pruritic	1	1
	Skin discolouration	13	5
	Skin warm	1	
	Urticaria	1	1
	Yellow skin	2	
Vascular disorders	Pallor	17	9
	Vasodilatation		1
	Total	647	398

Appendix 6

Overview of reported non-serious AEFIs per SOC Vaxelis cohort (January 1, 2019 up to and including June 30, 2020) and Infanrix hexa cohort (January 1, 2018 up to and including June 30, 2019) of vaccination number 2 of the old schedule.

		Vaxelis	Infanrix hexa
	Number of serious cases	**N= 87 Reports**	**N= 63 Reports**
System Organ Class (SOC)	**Preferred term (Pt)**	**number AEFIs**	**number AEFIs**
Ear and labyrinth disorders	Hyperacusis	1	
Eye disorders	Eye inflammation		**1**
	Eye swelling	1	
	Swelling of eyelid		1
Gastrointestinal disorders	Abdominal pain	3	1
	Constipation	**2**	2
	Diarrhoea	5	1
	Discoloured vomit	1	
	Faeces discoloured	2	
	Flatulence	1	1
	Frequent bowel movements	**1**	1
	Gastrointestinal pain	1	
	Gastrooesophageal reflux disease	1	
	Lip swelling	1	
	Nausea		1
	Regurgitation	1	
	Retching		1
	Swollen tongue	1	
	Vomiting	9	4
General disorders and administration site conditions	Extensive swelling of vaccinated limb	1	2
local reactions	Injection site discharge		1
	Injection site discolouration		1
	Injection site erythema	17	13
	Injection site granuloma		1
	Injection site haematoma		1
	Injection site induration	2	6
	Injection site inflammation	15	9
	Injection site mass		1
	Injection site nodule	1	2
	Injection site pain	13	10
	Injection site rash	1	1
	Injection site swelling	19	10
	Injection site warmth	12	5
General disorders and administration site conditions	Asthenia	2	
systemic reactions	Crying	32	8
	Fatigue	5	2
	Hyperpyrexia	1	
	Malaise	2	1
	Pain	5	
	Peripheral swelling	1	
	Pyrexia	33	23
	Screaming	3	
Infections and infestations	Erythema infectiosum		1
	Gastrointestinal viral infection		1
	Nasopharyngitis	2	
Investigations	Body temperature decreased	1	2
	Body temperature increased	4	3
	Faecal volume decreased	1	
Metabolism and nutrition disorders	Decreased appetite	9	3
	Hypophagia	1	
	Increased appetite		1
Musculoskeletal and connective tissue disorders	Infantile back arching	1	
	Pain in extremity	1	
	Posture abnormal	1	
Nervous system disorders	Apparent life threatening event		1
	Depressed level of consciousness	1	1
	Drooling	1	
	Headache	1	1
	Hypertonia	3	1
	Hyporesponsive to stimuli	1	
	Hypotonia	2	1
	Hypotonic-hyporesponsive episode	1	1
	Slow response to stimuli	1	1
	Somnolence	6	2
	Syncope	2	
	Unresponsive to stimuli		1
Psychiatric disorders	Abnormal behaviour	2	
	Agitation	1	
	Apathy	1	1
	Insomnia	9	4

	Irritability	2	
	Listless	5	
	Restlessness	6	
	Sleep disorder	2	
	Trichotillomania	1	
Respiratory, thoracic and mediastinal disorders	Apnoeic attack	1	
	Cough		1
	Dyspnoea	2	1
	Respiration abnormal	2	1
Skin and subcutaneous tissue disorders	Eczema	1	
	Erythema	2	2
	Nail discolouration	1	
	Petechiae	1	1
	Pruritus	1	
	Purpura		1
	Rash	2	1
	Rash erythematous	1	2
	Rash macular		2
	Rash papular	1	
	Skin discolouration	3	1
	Urticaria	1	
Vascular disorders	Pallor	5	2
	Total	289	152

Appendix 7

Overview of reported non-serious AEFIs per SOC Vaxelis cohort (January 1, 2019 up to and including June 30, 2020) and Infanrix hexa cohort (January 1, 2018 up to and including June 30, 2019) of vaccination number 3 of the old schedule.

		Vaxelis	Infanrix hexa
	Number of serious cases	N= 79 Reports	N= 95 Reports
System Organ Class (SOC)	Preferred term (Pt)	number AEFIs	number AEFIs
Cardiac disorders	Cyanosis	1	
Eye disorders	Eye inflammation		1
	Eye movement disorder	1	1
Gastrointestinal disorders	Abdominal pain	2	1
	Constipation	1	
	Diarrhoea	2	4
	Flatulence	1	1
	Haematochezia		1
	Vomiting	11	9
General disorders and administration site conditions	Extensive swelling of vaccinated limb	1	1
local reactions	Injection site discolouration	2	
	Injection site erythema	8	14
	Injection site haemorrhage	1	1
	Injection site induration		4
	Injection site inflammation	6	10
	Injection site nodule	2	2
	Injection site pain	7	7
	Injection site pruritus		1
	Injection site rash	1	1
	Injection site swelling	10	12
	Injection site urticaria	1	
	Injection site warmth	4	5
General disorders and administration site conditions	Crying	32	17
systemic reactions	Fatigue	4	
	Hyperpyrexia	1	3
	Malaise	3	1
	Moaning	1	
	Pain	3	2
	Peripheral swelling		1
	Pyrexia	33	57
	Screaming	1	
	Swelling	1	1
	Swelling face	1	
Infections and infestations	Injection site infection		1
	Nasopharyngitis	1	1
	Urinary tract infection		1
Injury, poisoning and procedural complications	Subcutaneous haematoma	1	
Investigations	Body temperature decreased	1	1
	Body temperature increased	2	1
	Respiratory rate increased		1
Metabolism and nutrition disorders	Decreased appetite	6	5
	Fluid intake reduced	1	
	Increased appetite		2
Musculoskeletal and connective tissue disorders	Infantile back arching	1	
	Muscle spasms		1
	Muscle twitching	1	
	Myalgia	1	
	Pain in extremity	2	1
Nervous system disorders	Febrile convulsion	1	1
	Fontanelle bulging		1
	Headache		1
	Hypersomnia	1	1
	Hypertonia	1	
	Hyporesponsive to stimuli	1	2
	Hypotonia	2	2
	Hypotonic-hyporesponsive episode	3	3
	Opisthotonus	1	
	Petit mal epilepsy	1	
	Poor quality sleep		1
	Seizure	1	2
	Somnolence	11	
	Syncope	2	
Psychiatric disorders	Apathy	1	2
	Behaviour disorder		1
	Insomnia	3	
	Listless	4	4
	Restlessness	4	3
	Staring		1
Renal and urinary disorders	Micturition frequency decreased	1	
Respiratory, thoracic and mediastinal disorders	Asthma		1
	Cough	1	

	Dyspnoea	4	1
	Irregular breathing	1	1
	Productive cough	1	
	Rhinorrhoea	2	
Skin and subcutaneous tissue disorders	Angioedema		1
	Eczema	1	1
	Erythema	1	3
	Erythema multiforme		1
	Petechiae	2	3
	Rash	3	6
	Rash erythematous		2
	Rash macular	1	3
	Rash maculo-papular	1	
	Rash papular	3	
	Rash pruritic	1	
	Skin discolouration	5	6
	Urticaria	1	1
Vascular disorders	Pallor	3	3
	Vasodilatation	1	
	Total	229	231

Appendix 8

Overview of reported non-serious AEFIs per SOC Vaxelis cohort (January 1, 2019 up to and including June 30, 2020) and Infanrix hexa cohort (January 1, 2018 up to and including June 30, 2019) of the first booster vaccination (age 11 months; vaccination number 4 of the old schedule / C of the new schedule).

		Vaxelis	Infanrix hexa
	Number of serious cases	**N= 104 Reports**	**N= 125**
System Organ Class (SOC)	**Preferred term (Pt)**	**number AEFIs**	**number AEFIs**
Cardiac disorders	Cyanosis		**2**
Ear and labyrinth disorders	Ear swelling	1	
Eye disorders	Eye inflammation		1
	Eye movement disorder	1	
	Eye swelling	**1**	
	Gaze palsy	1	
Gastrointestinal disorders	Constipation	1	
	Diarrhoea	5	4
	Nausea	3	
	Retching	**1**	
	Vomiting	21	6
General disorders and administration site conditions	Administration site induration		1
local reactions	Extensive swelling of vaccinated limb	4	5
	Injected limb mobility decreased	1	
	Injection site bruising		2
	Injection site discolouration	2	4
	Injection site discomfort	2	1
	Injection site erythema	35	54
	Injection site haematoma	2	2
	Injection site induration	3	4
	Injection site inflammation	31	51
	Injection site nodule	2	1
	Injection site pain	15	33
	Injection site papule		1
	Injection site pruritus	2	5
	Injection site rash	2	
	Injection site reaction		1
	Injection site swelling	30	51
	Injection site vesicles		1
	Injection site warmth	18	40
General disorders and administration site conditions	Chills	1	1
systemic reactions	Condition aggravated	1	
	Crying	24	19
	Fatigue	3	2
	Gait disturbance	2	
	Hyperpyrexia	2	1
	Malaise	3	2
	Oedema peripheral	1	
	Pain	3	1
	Peripheral swelling	2	
	Pyrexia	45	70
	Screaming	1	1
	Swelling face	1	
	Thirst decreased	1	
Immune system disorders	Food allergy	1	
Infections and infestations	Ear infection	1	1
	Gianotti-Crosti syndrome		1
	Injection site abscess		1
	Injection site pustule		1
	Nasopharyngitis	2	1
	Respiratory tract infection	1	
	Subglottic laryngitis		1
Injury, poisoning and procedural complications	Fall		1
Investigations	Body temperature increased	4	4
Metabolism and nutrition disorders	Decreased appetite	8	7
Musculoskeletal and connective tissue disorders	Arthritis	1	
	Limb discomfort	1	
	Mobility decreased	1	
	Muscular weakness	2	
	Musculoskeletal stiffness		1
	Neck deformity	1	
	Pain in extremity	6	2
Nervous system disorders	Dizziness		1
	Febrile convulsion	4	7
	Headache	1	2
	Hyporesponsive to stimuli	2	
	Myoclonus		2
	Poor quality sleep	1	1
	Somnolence	2	2
	Syncope	1	
	Tremor	1	

Psychiatric disorders	Abnormal behaviour	1	
	Apathy	1	2
	Insomnia	5	4
	Listless	10	7
	Nightmare		1
	Restlessness	1	1
	Sleep disorder	1	2
Renal and urinary disorders	Micturition frequency decreased	1	
Respiratory, thoracic and mediastinal disorders	Cough	1	
	Dyspnoea		1
	Irregular breathing		1
	Oropharyngeal pain		1
	Rhinorrhoea	2	
	Tachypnoea		1
	Wheezing		1
Skin and subcutaneous tissue disorders	Cold sweat		1
	Eczema	1	1
	Erythema	4	1
	Hyperhidrosis	1	
	Livedo reticularis		**1**
	Petechiae	1	1
	Pruritus	**1**	
	Rash	2	**8**
	Rash erythematous	3	**2**
	Rash macular	3	1
	Rash papular	1	1
	Skin discolouration	3	2
	Urticaria	**3**	3
Vascular disorders	Pallor	3	2
	Peripheral coldness	2	1
	Total	366	450

Appendix 9

Overview of reported non-serious AEFIs (priming vaccination moment A and B) per SOC Vaxelis cohort (January 1, 2019 up to and including June 30, 2020).

	vaccination moment	A	B
	Number of serious cases	N= 82 Reports	N= 38 Reports
System Organ Class (SOC)	Preferred term (Pt)	number AEFIs	number AEFIs
Cardiac disorders	Cyanosis		**1**
Eye disorders	Gaze palsy		**1**
Gastrointestinal disorders	Abdominal pain	1	1
	Constipation	1	
	Diarrhoea	4	
	Flatulence	**1**	1
	Frequent bowel movements	2	
	Gastrointestinal pain		1
	Infrequent bowel movements	1	
	Vomiting	5	2
General disorders and administration site conditions	Extensive swelling of vaccinated limb	**1**	1
local reactions	Injection site discomfort		1
	Injection site erythema	9	4
	Injection site induration	1	
	Injection site inflammation	8	3
	Injection site pain	10	2
	Injection site rash		1
	Injection site swelling	11	4
	Injection site warmth	4	
General disorders and administration site conditions	Crying	37	8
systemic reactions	Decreased activity	1	
	Fatigue	3	
	General physical health deterioration	1	
	High-pitched crying	1	
	Hyperpyrexia		1
	Malaise		2
	Moaning	2	1
	Oedema peripheral	1	
	Pain	2	
	Peripheral swelling	1	
	Pyrexia	35	25
	Screaming	4	
Infections and infestations	Injection site abscess		1
Investigations	Body temperature fluctuation	1	1
	Body temperature increased	5	3
Metabolism and nutrition disorders	Decreased appetite	8	1
	Fluid intake reduced		1
	Increased appetite	1	
Musculoskeletal and connective tissue disorders	Muscle twitching		1
	Pain in extremity	2	1
Nervous system disorders	Febrile convulsion		1
	Hypersomnia	1	
	Hypertonia	2	
	Hypotonia	1	
	Hypotonic-hyporesponsive episode	2	
	Loss of consciousness	1	
	Myoclonus	1	
	Poor quality sleep	2	
	Psychomotor hyperactivity	1	
	Somnolence	7	1
Psychiatric disorders	Abnormal behaviour	3	
	Abnormal dreams	1	
	Breath holding	1	
	Conversion disorder		1
	Delirium febrile	1	
	Insomnia	2	
	Listless	4	3
	Panic reaction	1	
	Restlessness	3	1
	Staring		1
Renal and urinary disorders	Anuria		1
Respiratory, thoracic and mediastinal disorders	Apnoea		1
	Choking		1
	Cough	1	
	Dyspnoea		1
	Nasal congestion	1	
	Productive cough		1
Skin and subcutaneous tissue disorders	Dermatitis atopic	1	
	Eczema	2	1
	Erythema	1	
	Hyperhidrosis	1	
	Livedo reticularis		1
	Petechiae	1	1

	Photosensitivity reaction	1	
	Pruritus	2	
	Purpura	2	
	Rash	2	2
	Rash macular	1	1
	Rash papular		1
	Rash vesicular	1	
	Skin discolouration	5	5
	Urticaria	3	1
Vascular disorders	Pallor	3	1
	Peripheral coldness		1
	Total	226	97