

**Long-lasting adverse events following immunization with Cervarix®**

**Update 2016**

## Summary

Since the introduction of the HPV-vaccine Cervarix® to the National Immunization Program in 2009, The Netherlands Pharmacovigilance Centre Lareb received 1436 reports of AEFIs following immunization with Cervarix®, including 346 reports of long-lasting AEFIs (duration of two months or more).

The majority of the reports were received in the introduction year of Cervarix® to the National Immunization Program. Most reports concern short-term AEFIs. The majority of the reports that concern long-lasting AEFIs were received after media attention on the HPV-vaccine in 2012 and 2015. The reporting rate of long-lasting AEFIs per birth cohort is constant, about 4-8 per 10,000 vaccinated girls. Since Lareb depends on spontaneous reports, it is not possible to estimate the actual prevalence of long-lasting AEFIs after vaccination with Cervarix®.

Fatigue was the most frequently reported long-lasting AEFI (N = 256). Several combinations of frequently reported AEFIs were found, but there was no consistent combination pattern in all the reports of long-lasting AEFIs. In 2015 The Netherlands Pharmacovigilance Centre Lareb did a follow-up survey to long-lasting reports. This follow-up survey showed that these long-lasting, unexplained symptoms have considerable impact on the lives of these girls and the lives of their family members. No cause for the complaints could be found and most of the girls were not recovered at the moment of last contact with Lareb. This new update provides no new insights compared with the conclusions of the report of December 2015.

A causal relation between Cervarix® vaccination and long-lasting symptoms can not be concluded nor excluded based on the analysis of these reports. In order to study whether long-lasting fatigue occurs more often in vaccinated girls than in unvaccinated girls and in order to determine the presence and strength of a causal relationship, an epidemiological research is recommended. The National Institute for Public Health and the Environment (RIVM) already started a study.

## Samenvatting

Sinds de introductie van het HPV-vaccin Cervarix® in het Rijksvaccinatieprogramma in 2009, ontving Bijwerkingencentrum Lareb 1436 meldingen van Adverse Events Following Immunization (AEFIs) in relatie tot Cervarix®, waaronder 346 meldingen van langdurige AEFIs (duur van twee maanden of meer).

De meeste Cervarix® meldingen werden in het introductiejaar ontvangen en betreffen voornamelijk kortdurende klachten. De meldingen van langdurige klachten ontving Lareb naar aanleiding van media-aandacht rondom het HPV-vaccin in 2012 en 2015. Het aantal meldingen van langdurige klachten gedurende de tijd is echter constant, ongeveer 4-8 per 10,000 gevaccineerde meisjes. Het is niet mogelijk om van deze klachten de prevalentie te bepalen, aangezien het spontane meldingen betreft.

In de 346 meldingen met langdurige AEFIs werd langdurige vermoeidheid het meest genoemd (N=256). Verschillende patronen van combinaties van langdurige klachten werden gevonden, echter was er geen enkel patroon consistent. In 2015 heeft Bijwerkingencentrum Lareb een follow-up studie uitgevoerd naar meldingen van langdurige klachten. De gerapporteerde langdurige klachten hebben een aanzienlijke impact op het dagelijkse leven van de meisjes en hun naasten. Dit rapport met een update van de meldingen, biedt geen nieuwe inzichten in vergelijking met de conclusies van december 2015.

Op basis van de analyse van de gemelde langdurige AEFIs kan een causaal verband tussen Cervarix® vaccinatie en deze klachten noch worden uitgesloten noch worden aangetoond. Om te onderzoeken of langdurige vermoeidheid vaker voorkomt bij gevaccineerde meisjes in vergelijking met niet gevaccineerde meisjes en om de aanwezigheid en de sterkte van een causaal verband te kunnen bepalen, wordt een nader epidemiologisch onderzoek aanbevolen. Inmiddels is het RIVM met een onderzoek gestart.

## 1. Introduction

Cervarix<sup>®</sup>, Gardasil<sup>®</sup> and Gardasil 9<sup>®</sup> are vaccines registered for immunization against infection with human papillomavirus (HPV). Cervarix<sup>®</sup> leads to active immunization against HPV types 16 and 18. Gardasil<sup>®</sup> leads to active immunization against types 6, 11, 16 and 18 and Gardasil 9<sup>®</sup> against types 6, 11, 16, 18, 31, 33, 45, 52 and 58 [1]. In 2009 Cervarix<sup>®</sup> was added to the Dutch national immunization program for prevention of cervical cancer. All girls living in the Netherlands receive an invitation for vaccination in the year they turn 13 years old. In 2009, the year of introduction, the vaccination was offered to girls of the birth cohorts 1993-1996. Since 2010 the vaccination is offered on yearly basis to only one birth cohort. Until 2014 girls received three HPV-vaccinations in total. Between the first and second vaccination there was a one month interval and between the second and third an interval of five months. In 2014 the number of HPV-vaccinations was reduced to two, with five months between vaccinations. The vaccination coverage has increased over the years. While the vaccination coverage in the birth cohort 1993-1996 was 52.3%, the coverage in the birth cohort of 2000 was 61.0% in 2015 [2,3].

In 2011 the Netherlands Pharmacovigilance Centre Lareb published an overview of the adverse events following immunization (AEFIs) reported in association with Cervarix<sup>®</sup> [4] and in 2013 an overview of reports of long-lasting fatigue associated with Cervarix<sup>®</sup> [5].

In 2013 and 2014 there has been media attention in Denmark concerning two conditions in relation to vaccination against HPV infection: complex regional pain syndrome (CRPS), a chronic pain condition affecting the limbs and Postural Orthostatic Tachycardia Syndrome (POTS), a condition where the heart rate increases abnormally after sitting or standing up, causing symptoms such as dizziness and fainting, as well as headache, chest pain and weakness [7,8]. At the request of Denmark, the European Medicines Agency (EMA) has initiated a review of HPV vaccines to further clarify aspects of their safety profile. This review is being carried out by the Pharmacovigilance Risk Assessment Committee (PRAC).

At the end of July 2015 Lareb published an update of the previous overview of all AEFIs reported in relation to Cervarix<sup>®</sup> [9]. Following this release, concerns about the safety of the HPV-vaccine was picked up by national media. In the month following this media attention, Lareb received more than one hundred reports on Cervarix<sup>®</sup>. Lareb decided to enhance the clinical documentation level of both the newly received and the older reports concerning long-lasting (duration of 2 months or more) AEFIs by obtaining additional information through intensive follow up. The report gave an updated overview of all reports and an analysis of all cases of long-lasting AEFIs in association with Cervarix<sup>®</sup> that were received between 1 January 2009 and 15 October 2015. The report was published in December 2015 [6]. This report gives an overview of reports received between 1 January 2009 and 31 October 2016.

## 2. Overview of all reports of adverse events following immunization with Cervarix®

### Reporting pattern 2009 - 2016

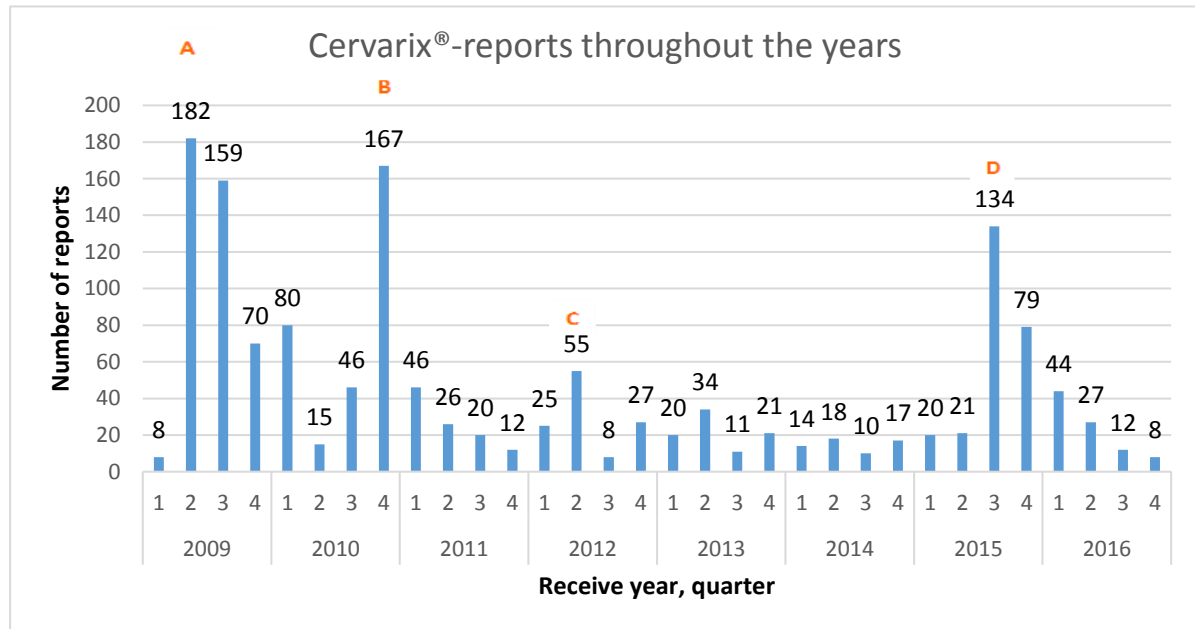


figure 1 Number of Cervarix®-reports throughout the years. **A:** Introduction of Cervarix® to the Dutch National immunization program, media-attention and awareness for new AEFIs. **B:** Transition of Cervarix®-reports from RIVM to Lareb: remaining reports entered in the Lareb ADR-database. **C:** 20-03-2012 Article on AEFIs following HPV-vaccination in a Dutch newspaper “De Telegraaf” [10]. **D:** 29-07-2015 Lareb announces further investigation of possible long-lasting AEFIs in relation to Cervarix® on Dutch radio [11,12].

### Frequently reported AEFIs 2009 – 2016

Table 1 Top 10 reported AEFIs in association with Cervarix® Receive date: 01-01-2009 to 31-10-2016.

AEFIs	Times reported
Headache	562
Pain	409
Fatigue	383
Pyrexia	380
Dizziness	341
Nausea	332
Myalgia	178
Inflammation	164
Abdominal pain	136
Malaise	132

### 3. Reports concerning long-lasting AEFIs in association with Cervarix®

#### Selection and follow-up

In the period from 1 January 2009 to 31 October 2016 a total of 1436 Cervarix®-reports were received. A review was conducted only on reports that concerned possible AEFIs following Cervarix® vaccination given in the context of the Dutch National Vaccination Program (vaccination date  $\geq$  01-01-2009) to girls with a birthdate  $\geq$  01-01-1993. To detect reports concerning long-lasting AEFIs, all reports with AEFIs which lasted two months or more, where selected as long-lasting. Occasionally, complaints were already existent before vaccinations were given, these cases were excluded. When complaints worsened after vaccination, the report was included. It should be noted that several reports concerned AEFIs that at the time of last contact didn't last two months yet, but that the girls hadn't recovered either. Because these AEFIs are potentially long-lasting, they were also selected. The duration of these AEFIs was rated as "Unknown". After this selection process doubtful cases were discussed between colleagues. Eventually 346 reports were selected as long-lasting.

#### Reports

Most reports of long-lasting AEFIs were received in the third quarter of 2015 after media attention on the Dutch radio (figure 2).

The majority of the reporters mentioned that they were not sure about the exactness of vaccination dates. Therefore all dates of vaccination and batch numbers were verified via the Vaccination Registry of the National Institute for Public Health and the Environment (RIVM) after obtaining permission from the vaccinated girl and/or her parents. Figure 2 gives an overview of the number of reports concerning the long-lasting and all other AEFIs per year of vaccination.

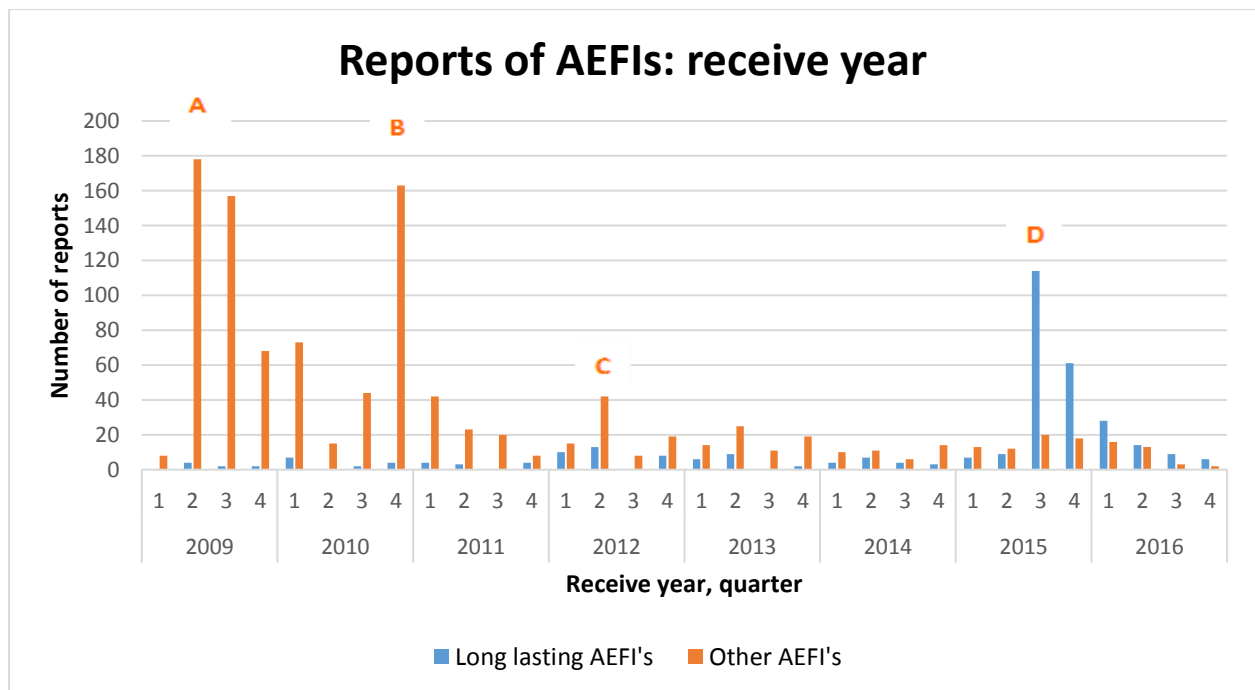


Figure 2. Receive year of reports concerning long-lasting AEFIs in association with Cervarix®. Receive date: 01-01-2009 to 31-10-2016. **A:** Introduction of Cervarix® to the Dutch National immunization program, media-attention and awareness for new AEFIs. **B:** Transition of Cervarix®-reports from the RIVM to Lareb: remaining reports entered in the Lareb ADR-database. **C:** 20-03-2012 Article on AEFIs following HPV-vaccination in a Dutch newspaper "De Telegraaf" [10]. **D:** 29-07-2015 Pharmacovigilance Center Lareb announces further investigation on possible long-lasting AEFIs in relation to Cervarix® on Dutch radio [11,12].

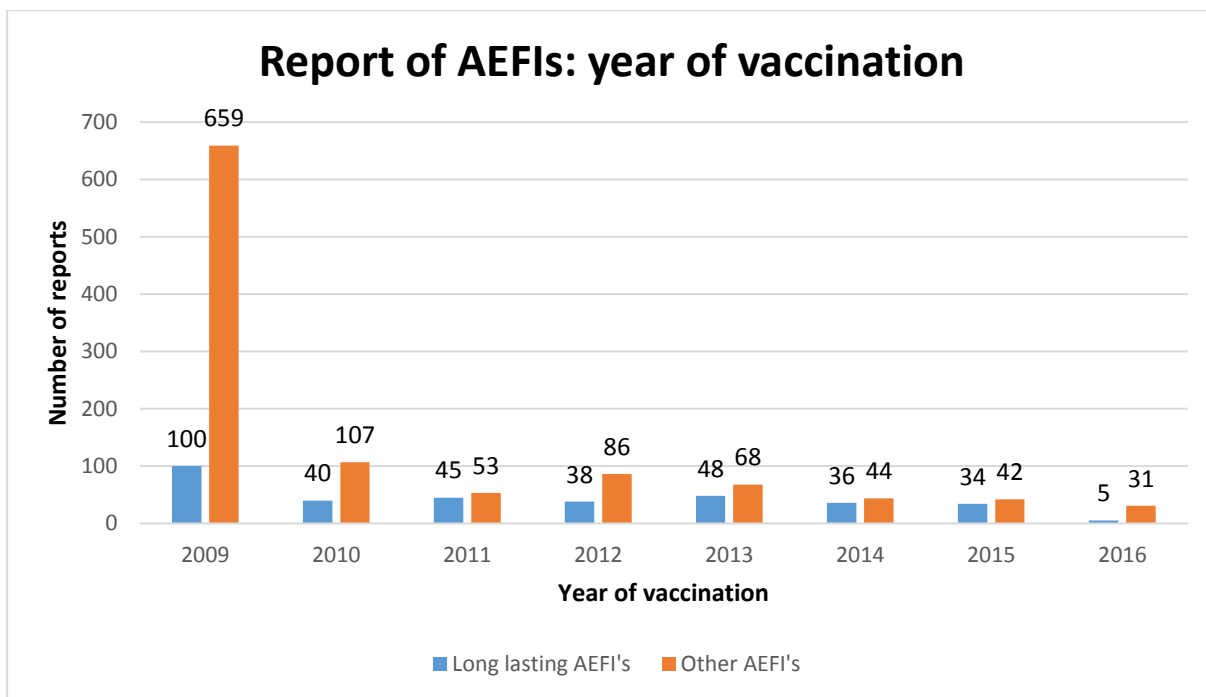


Figure 3. Year of vaccination with Cervarix® of girls experiencing AEFIs: Long-lasting and other AEFIs.

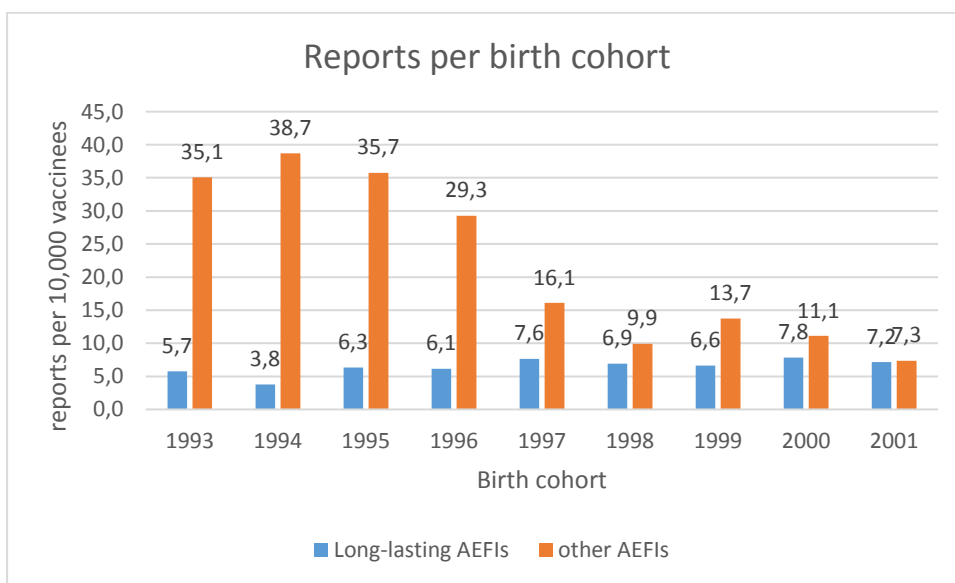


Figure 4. Number of reports per 10,000 vaccinees per birth cohort with complete Cervarix®-vaccination. Long-lasting and all other AEFIs.

In 2009 four birth cohorts were vaccinated. For this reason we looked at the reports per birth cohort. For the birth cohorts 1993-2001 information was obtained about the cohort size and the number of girls vaccinated. The birth cohorts from 1993 to 2001 fluctuate between 96,012 girls to 100,210 girls. Over the same period the vaccination participation has increased from 49% to 61%. For the birth cohorts 2002 this information is not yet available. To make successive birth cohorts comparable, we calculated the number of reports per 10,000 vaccinees. Figure 4 shows the number of long-lasting AEFIs and the number of all other AEFIs reported per 10,000 vaccinees with complete Cervarix®-vaccination (three vaccinations in total) per birth cohort [3,13-16]. The number of reports concerning long-lasting AEFIs is almost constant, about 4 - 8 per 10,000 vaccinees. Girls from birth cohorts 1993 to 1996 all vaccinated in 2009, have reported more other AEFIs per 10,000 vaccinees in comparison to later birth cohorts.

## Frequently reported long-lasting AEFIs

In the majority of the received reports, there was more than one long-lasting adverse event reported. In total 1167 long-lasting, medically unexplained AEFIs were reported, giving an average of 3.4 AEFIs per report. Most reported long-lasting AEFI was fatigue. An overview of long-lasting AEFIs that were reported 5 times or more is given in Appendix A.

Some of the AEFIs were clustered because they concerned different descriptions of the same type of complaint. The following clusterings were applied: “Headache” represents the cluster consisting of headache and migraine (with aura). “Dizziness” represents dizziness, postural dizziness, exertional dizziness and vertigo. “Syncope” represents syncope and presyncope. “Palpitations” represents palpitations and tachycardia. “Musculoskeletal discomfort” represents myalgia (aggravated), arthralgia (aggravated), muscular weakness, pain in extremity, musculoskeletal pain, musculoskeletal discomfort, back pain, fibromyalgia, patellofemoral pain syndrome and neck pain. “Menstruation disorder” represents menstrual disorder, dysmenorrhea, amenorrhoea, menstruation irregular and menorrhagia. Table 2 shows the top 10 of most reported long-lasting clustered AEFIs. More than 70% of the long-lasting reports contain fatigue and over 50% of these reports contain headache.

Table 2. Top 10 clusters of reported long-lasting AEFIs in association with Cervarix®. Receive date: 01-01-2009 to 31-10-2016.

AEFIs	Times reported
Fatigue	256
Headache	181
Dizziness	117
Musculoskeletal discomfort	91
Syncope	56
Nausea	48
Menstruation disorder	23
Pyrexia	19
Malaise	14
Disturbance in attention	14

## Frequently reported combinations of long-lasting AEFIs

To investigate the relationship between the various AEFIs and to see if distinct patterns of AEFIs might exist, it was examined how many reports contained the same combination of AEFIs. All possible combinations are presented in Appendix B. The most reported combinations are visualized in the figures below.

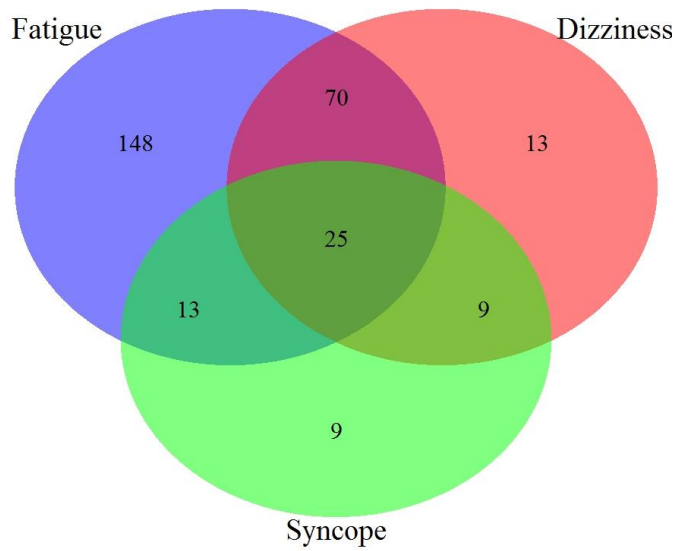


Figure 5a. Reported combinations of the AEFIs "Fatigue" and/or "Syncope" and/or "Dizziness".

25 Reports had the combination of fatigue, syncope and dizziness as reported AEFIs.

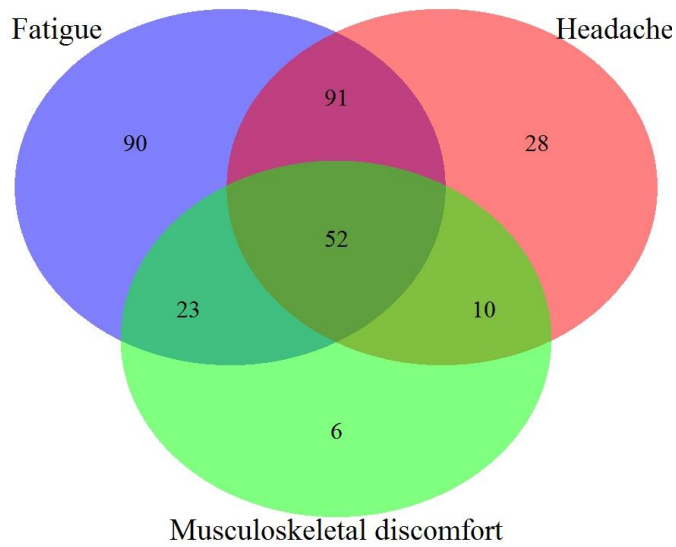


Figure 5b. Reported combinations of the AEFIs "Fatigue" and/or "Headache" and/or "Musculoskeletal discomfort".

52 Reports had the combination of fatigue, headache and musculoskeletal discomfort as reported AEFIs.



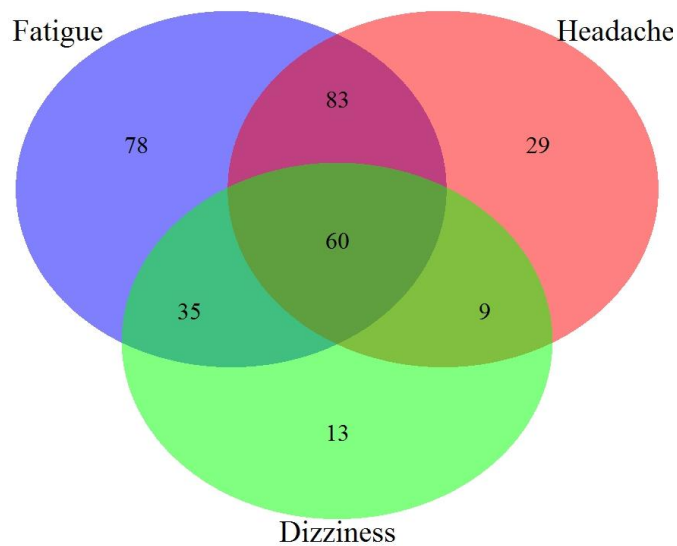


Figure 5c. Reported combinations of the AEFIs "Fatigue" and/or "Headache" and/or "Dizziness".

60 Reports had the combination of fatigue, headache and dizziness as reported AEFIs.

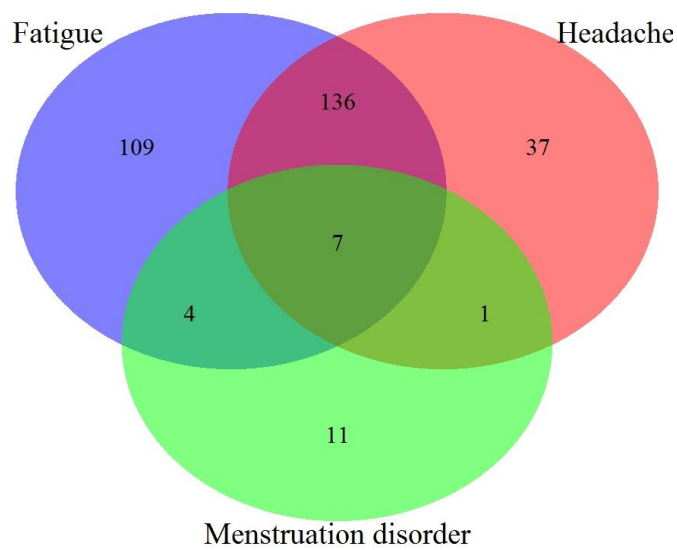


Figure 5d. Reported combinations of the AEFIs "Fatigue" and/or "Headache" and/or "Menstruation disorder".

Seven reports had the combination fatigue, headache and menstrual disorder as reported AEFIs.

## Latency to onset

The majority of reports were regarding multiple long-lasting adverse events, often with a varying time to onset for each event. The latency per reports was calculated. The latency per report was defined as the time between the suspect injection moment and the onset of the (first) long-lasting adverse event. The suspect injection moment was defined as the most recent injection prior to the onset of the (first) long-lasting adverse event, unless the reporter indicated otherwise. In order to verify the start and the first presentation of the symptoms, medical records of the general practitioner and specialist letters were examined when available. Occasionally, complaints were already existent before vaccinations were given, these cases were excluded. When complaints worsened after vaccination, the report was included. Figure 6 gives an overview of the reported latency to onset of long-lasting AEFIs per report. The majority of the reports containing long-lasting AEFIs, contains at least one AEFI that emerges in the first year following vaccination.

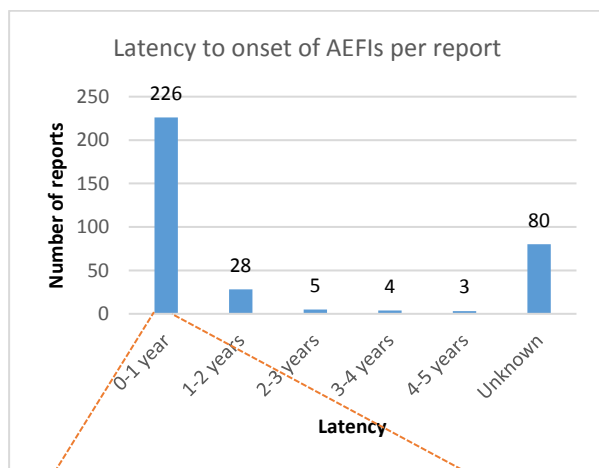


Figure 6a. Latency to onset of reported AEFIs in reports with long lasting AEFIs in association with Cervarix® Receive date: 01-01-2009 to 31-10-2016.

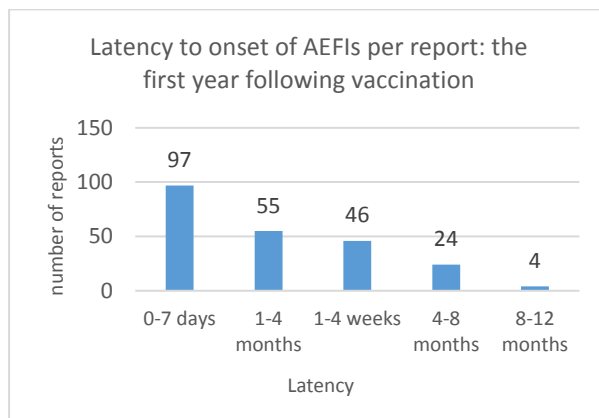


Figure 6b. Latency to onset of reported AEFIs in reports with long lasting AEFIs in association with Cervarix® – first year after vaccination. Receive date 01-01-2009 to 31-10-2016.

The majority of the reports contains information of latency to onset per AEFI. Since most reports concerning adverse reactions that arose a few years earlier and most side effects gradually arose, the latency times are not entirely reliable. Where possible is the latency time, on the basis of information obtained during telephone interview or on the basis of medical data of the patient, updated. Figure 7 gives an overview of the latency time to onset per AEFI of long-lasting AEFIs.

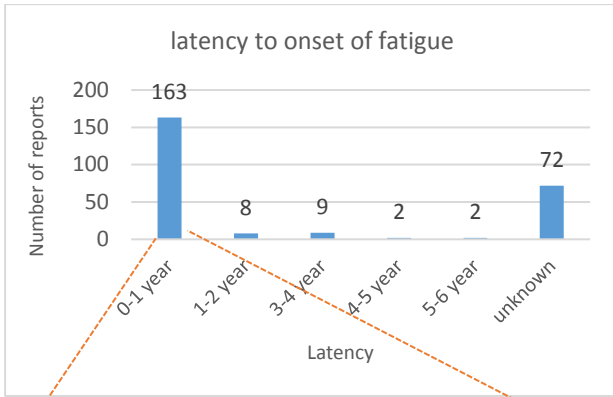


Figure 7a. Latency to onset of reported fatigue in reports with long lasting AEFIs in association with Cervarix® Receive date: 01-01-2009 to 31-10-2016.

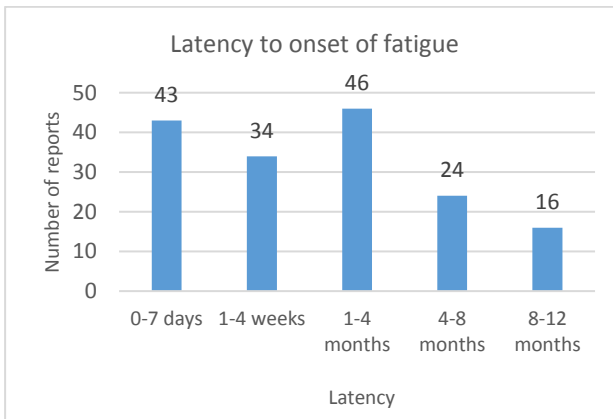


Figure 7b. Latency to onset of reported fatigue in reports with long lasting AEFIs in association with Cervarix® – first year after vaccination. Receive date 01-01-2009 to 31-10-2016.

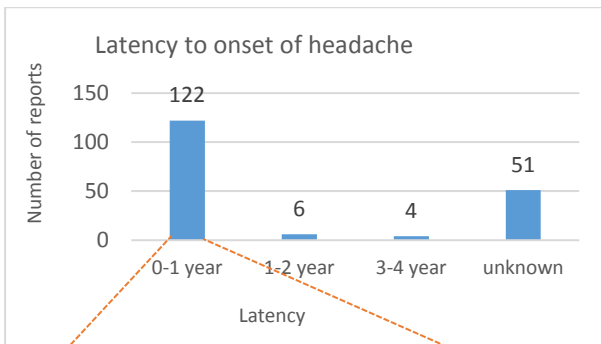


Figure 8a. Latency to onset of reported headache in reports with long lasting AEFIs in association with Cervarix® Receive date: 01-01-2009 to 31-10-2016

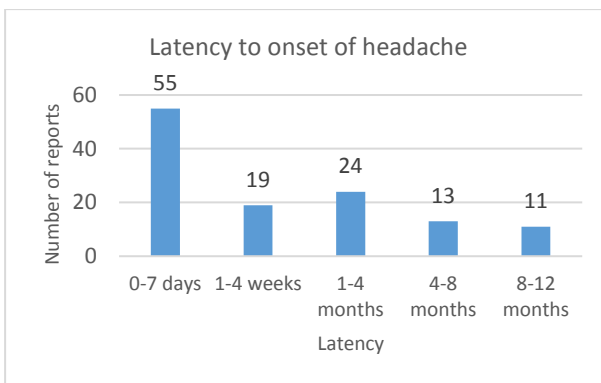


Figure 8b. Latency to onset of reported headache in reports with long lasting AEFIs in association with Cervarix® – first year after vaccination. Receive date 01-01-2009 to 31-10-2016.

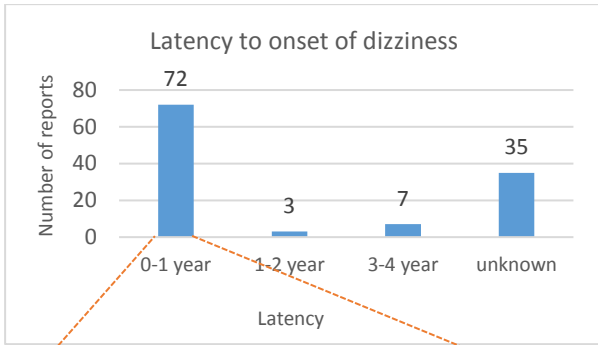


Figure 9a. Latency to onset of reported dizziness in reports with long lasting AEFIs in association with Cervarix® Receive date: 01-01-2009 to 31-10-2016

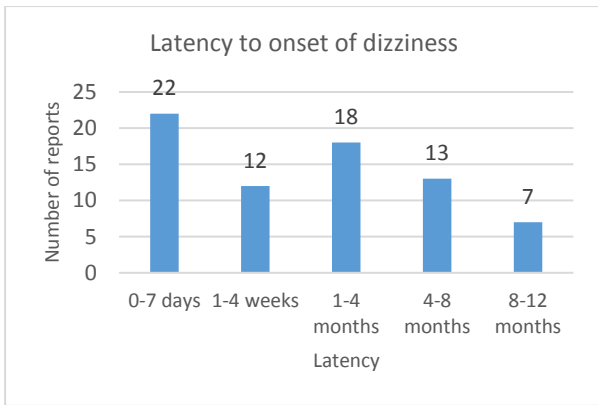


Figure 9b. Latency to onset of reported dizziness in reports with long lasting AEFIs in association with Cervarix® – first year after vaccination. Receive date 01-01-2009 to 31-10-2016.

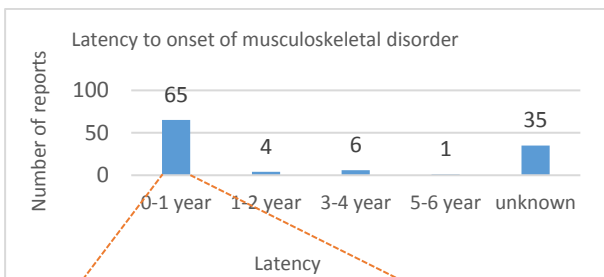


Figure 10a. Latency to onset of reported musculoskeletal disorder in reports with long lasting AEFIs in association with Cervarix® Receive date: 01-01-2009 to 31-10-2016

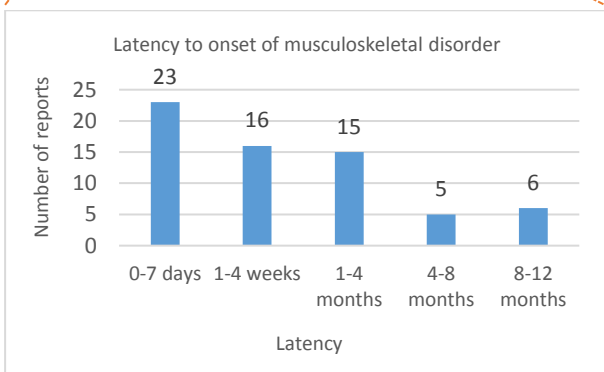


Figure 10b. Latency to onset of reported musculoskeletal disorder in reports with long lasting AEFIs in association with Cervarix® – first year after vaccination. Receive date 01-01-2009 to 31-10-2016.

## Duration and recovery

Duration was defined as the time between onset of the first long-lasting AEFI and either the recovery of the patient or if the patient did not fully recover, the date of the last contact with the Pharmacovigilance centre Lareb.

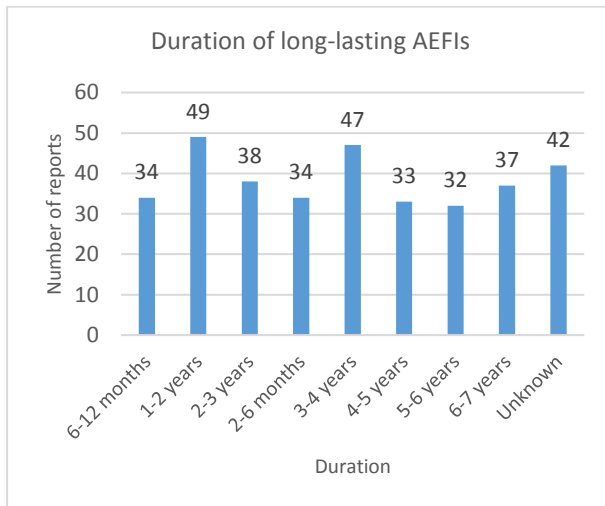


figure 11 Duration of reported long-lasting AEFIs in association with Cervarix®

Usually several complaints have been reported and these symptoms often have different recovery statuses. Therefore was decided to look at recovery of the patient as a whole. For example: when the recovery status of one or more of the reported complaints was "not recovered", "recovering" or "recovered with sequel", the overall recovery status was considered "not recovered".

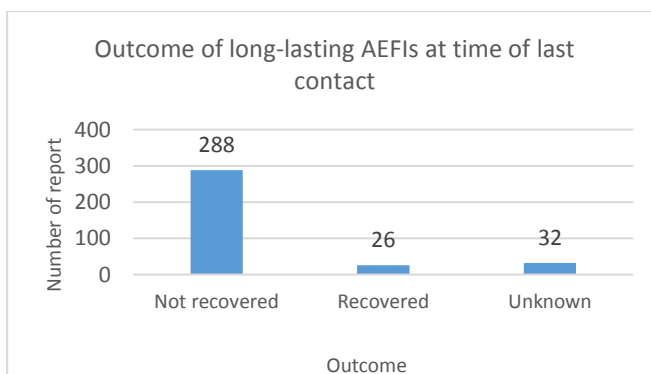


Figure 12. Outcome of reported long-lasting AEFIs in association with Cervarix® at time of last contact with Lareb.

## Vaccine batches

Since the introduction of Cervarix® in the Dutch National Immunization Programme in 2009, fourteen different batches are used. It was found that more than 50% of all Cervarix® reports originate from three batches. It was investigated whether there could be a batch-related problem. Based on information gathered on the size of the batches, the geographical distribution of the batches and the year in which the batches are used, a batch-related problem does not seem likely.

## 4. Discussion

Since the introduction of the HPV-vaccine to the Dutch National Immunization Program in 2009, the Dutch Pharmacovigilance Centre Lareb received 1436 reports of possible AEFIs following Cervarix<sup>®</sup>, including 346 reports of long-lasting AEFIs with a duration of 2 months or more. Most reports were received in the year of introduction of Cervarix<sup>®</sup> to the National Immunization Program and are mainly reports of short-term AEFIs. During the catch-up campaign in 2009 for girls born in the period 1993 to 1996 an intensive post-marketing surveillance was set up, such as reporting forms to register immediate occurring AEFIs on the location of vaccination and a web-based tolerability study (web-based questionnaire on local reactions and systemic AEFIs). This extra attention for AEFIs and the media attention on the introduction of Cervarix<sup>®</sup> could have contributed to the additional number of reports of short-term AEFIs [17].

The majority of the reports concerning long-lasting AEFIs was received after media attention in 2012 and 2015. These reports concerned vaccinations given over the whole period since the start of the program. The reporting rate of long-lasting AEFIs per birth cohort is constant, about 4 - 8 per 10,000 vaccinated girls. Since Lareb depends on spontaneous reports, it is not possible to estimate the actual prevalence of long-lasting AEFIs after vaccination with Cervarix<sup>®</sup>.

The most frequently reported long-lasting AEFI was fatigue (N = 256). Several combinations of frequently reported AEFIs were found, but there was no consistent combination pattern in all the reports of long-lasting AEFIs. One of the most reported combination of long-lasting AEFIs concerns fatigue combined with headache and musculoskeletal discomfort. This combination of complaints, including the fact that no medical explanation was found, are partially in line with the criteria for chronic fatigue syndrome used by the Dutch Institute for Healthcare Improvement (CBO) concerning diagnosis, treatment, support and assessment of patients with chronic fatigue syndrome (CFS) [18]. Although some reports concern symptoms which could be indicative of POTS or CRPS, in none of them there were indications for these diagnoses. Almost all girls with long-lasting complaints had not recovered at the moment of last contact with Lareb.

In the majority of the reports the vaccinations were given before the onset of complaints. Since most reports of long-lasting AEFIs have a reporting delay of three to six years and symptoms often gradually developed, it is difficult to estimate the latency accurately. There appeared to be no typical interval: onset varied from days to months and even a few years after vaccination.

Before the introduction of Cervarix<sup>®</sup> to the National Immunization Program chronic fatigue and other chronic complaints were well known symptoms in adolescence. In 1997 De Jong et al., Bazelmans et al. and Versluis et al. found a prevalence of 1-10 per 10,000 persons concerning fatigue [19-21]. These estimates were however based on different populations with different case definitions. Ter Wolbeek et al. performed a school-based study with questionnaires in adolescents and found that 20% of girls and 6% of boys reported severe fatigue, that was also long lasting in a considerable part of them [22]. In 2005, van der Linden et al. reported that the incidence of GP consultations for fatigue was 10 per 1000 for girls at the age of 10 years, and increased to 47 per 1000 for girls at the age of 15 (for boys these numbers were respectively 9 and 17 per 1000) [23].

Several studies have been done to investigate the possible relation between chronic fatigue syndrome and the vaccination: the MHRA in the United Kingdom performed "observed versus expected" analyses comparing the number of reports of fatigue syndromes to the expected number, using background rates calculated from health care databases and estimates of vaccination coverage. They found no increased risk for vaccinated girls to develop fatigues syndromes and the numbers of spontaneous reports were consistent with estimated background rates. Through ecological analysis and a self-controlled case series, they also compared the incidence rate of fatigue syndromes in girls before and after the start of the vaccination campaign and the risk in the year post-vaccination compared to other periods. They did not observe a change in incidence of fatigue

after introduction of the HPV vaccination, nor an increased risk using the self-controlled case series approach [24,25].

## Conclusion

Lareb has received a substantial number of reports concerning long-lasting AEFIs after vaccination with Cervarix®. The most frequently reported long-lasting AEFI was fatigue. This follow-up survey showed that these long-lasting, unexplained symptoms have considerable impact on the lives of these girls and the lives of their family members. Also no cause for the complaints could be found and most of the girls were not recovered at the moment of last contact with Lareb.

Based on the analysis of these reports a causal relation between Cervarix® vaccination and long-lasting symptoms can not be concluded nor excluded. In order to study whether long lasting fatigue occurs more often in vaccinated girls than in unvaccinated girls, an epidemiological study is recommended. The National Institute for Public Health and the Environment (RIVM) is preparing a study.

## References

1. European Medicines Agency (EMA). European public assessment reports for human medicines. (version date: 2015, access date: 9-9-2015) <http://www.ema.europa.eu/ema/>.
2. Rijksinstituut voor Volksgezondheid en Milieu. Vaccinatiepercentage HPV vaccinaties van adolescente meisjes (gemeten op leeftijd van 14 jaar), 2011-2014. (version date: 1-10-2014, access date: 9-9-2015) <http://www.zorgatlas.nl/preventie/vaccinaties-en-screening/hpv-vaccinatiegraad-per-gemeente/>.
3. van Lier EA et al. Vaccinatiegraad Rijksvaccinatieprogramma Nederland Verslagjaar 2015. Rijksinstituut voor Volksgezondheid en Milieu (RIVM). 2015;
4. Netherlands Pharmacovigilance Centre Lareb. Overview adverse events following immunization in association with Cervarix. (version date: 29-9-2011, access date: 8-9-2015) [http://www.lareb.nl/Signalen/kwb\\_2010\\_2\\_cerva\\_2](http://www.lareb.nl/Signalen/kwb_2010_2_cerva_2).
5. Netherlands Pharmacovigilance Centre Lareb. Overview of reports of long-lasting fatigue following immunisation with Cervarix. (version date: 2013, access date: 17-11-2015) [http://www.lareb.nl/Signalen/KWB\\_2013\\_3\\_cerva](http://www.lareb.nl/Signalen/KWB_2013_3_cerva).
6. Netherlands Pharmacovigilance Centre Lareb. Long-lasting adverse events following immunization with Cervarix®.
7. Danish Health and Medicines Authority. Danish Pharmacovigilance Update. (version date: 1-5-2014, access date: 9-9-2015) <https://sundhedsstyrelsen.dk/en/news/2014/~media/6843B419214D4E82A5A966808D71D73C.ashx>.
8. European Medicines Agency. EMA to further clarify safety profile of human papillomavirus (HPV) vaccines. (version date: 13-7-2015, access date: 2-9-2015) [http://www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/news/2015/07/news\\_detail\\_002365.jsp&mid=WC0b01ac058004d5c1](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2015/07/news_detail_002365.jsp&mid=WC0b01ac058004d5c1).
9. Bijwerkingencentrum Lareb. Analyse van meldingen na HPV-vaccinatie (Cervarix®). (version date: 29-7-2015, access date: 3-9-2015) [http://www.lareb.nl/Signalen/Analyse\\_bijwerkingen\\_na\\_HPV-vaccinatie](http://www.lareb.nl/Signalen/Analyse_bijwerkingen_na_HPV-vaccinatie).
10. De Telegraaf. Klachten na meidenprik. (version date: 20-3-2012, access date: 8-9-2015) [http://www.telegraaf.nl/binnenland/20028512/\\_Klachten\\_na\\_meidenprik\\_.html](http://www.telegraaf.nl/binnenland/20028512/_Klachten_na_meidenprik_.html).
11. NPO Radio 1. Onderzoek naar bijwerkingen HPV-vaccinatie. (version date: 29-7-2015, access date: 8-9-2015) <http://www.radio1.nl/item/304282-Onderzoek-naar-bijwerkingen-HPV-vaccinatie.html>.
12. RTL nieuws. Is vaccin baarmoederhalskanker gevaarlijk? (version date: 29-7-2015, access date: 8-9-2015) <http://www.rtlnieuws.nl/nieuws/laatste-videos-nieuws/vaccin-baarmoederhalskanker-gevaarlijk>.
13. van Lier EA et al. Vaccinatiegraad Rijksvaccinatieprogramma Nederland Verslagjaar 2011. Rijksinstituut voor Volksgezondheid en Milieu (RIVM). 2011;
14. van Lier EA et al. Vaccinatiegraad Rijksvaccinatieprogramma Nederland Verslagjaar 2013. Rijksinstituut voor Volksgezondheid en Milieu (RIVM). 2013;
15. van Lier EA et al. Vaccinatiegraad Rijksvaccinatieprogramma Nederland Verslagjaar 2014. Rijksinstituut voor Volksgezondheid en Milieu (RIVM). 2014;
16. van Lier EA et al. Vaccinatiegraad Rijksvaccinatieprogramma Nederland Verslagjaar 2012. Rijksinstituut voor Volksgezondheid en Milieu. 2012;
17. 't Klooster TM, Kemmeren JM, Melker HE, and van der Maas NAT. Human Papillomavirus vaccination catch-up campaign in 2009 for girls born in 1993 to 1996 in the Netherlands. (version date: 2011, access



date: 23-11-2015)

[http://www.rivm.nl/dsresource?objectid=rivmp:24638&type=org&disposition=inline&ns\\_nc=1](http://www.rivm.nl/dsresource?objectid=rivmp:24638&type=org&disposition=inline&ns_nc=1).

18. CBO. Richtlijn Diagnose, behandeling, begeleiding en beoordeling van patiënten met het chronische vermoeidheidssyndroom (CVS). (version date: 2013, access date: 16-11-2015)  
[www.diliguide.nl/document/3435/file/pdf/](http://www.diliguide.nl/document/3435/file/pdf/).
19. de Jong LWAM, Prins JB, Fiselier THJW et al. Het chronische-vermoeidheidssyndroom bij jongeren. Nederlands Tijdschrift voor Geneeskunde. 1997; p.1513
20. Bazelmans E, Vercoulen JHMM, Galama JMD et al. Prevalentie van het chronische-vermoeidheidssyndroom en het primaire-fibromyalgiesyndroom in Nederland. Nederlands Tijdschrift voor Geneeskunde. 1997; p.1520
21. Versluis RG, de Waal MW, Opmeer C et al. Prevalentie van chronisch-vermoeidheidsyndroom in 4 huisartspraktijken in de regio Leiden. Nederlands Tijdschrift voor Geneeskunde. 1997; p.1523
22. ter Wolbeek M, van Doornen LJP, Kavelaars A et al. Severe fatigue in adolescents: a common phenomenon? Pediatrics. 2006; p.1078
23. van der Linden MW, van Suijlekom-Smit LWA, Schellevis FG, and van der Wouden JC. Het kind in de huisartspraktijk. Tweede nationale studie naar ziekten en verrichtingen in de huisartspraktijk. (version date: 2005, access date: 9-11-2015) <http://www.nivel.nl/sites/default/files/bestanden/ns2-kind-in-de-huisartspraktijk.pdf>.
24. Medicines and Healthcare products Regulatory Agency (MHRA). Cervarix HPV vaccine: update on UK safety experience at end of 4 years use in the HPV routine immunisation programme. (version date: 2012, access date: 17-11-2015) <https://assets.digital.cabinet-office.gov.uk/media/547307f540f0b6131200003d/con213228.pdf>.
25. Donegan K, Beau-lejdstrom R, King B et al. Bivalent human papillomavirus vaccine and the risk of fatigue syndromes in girls in the UK. Vaccine. 2013;

## Appendix A Long-lasting AEFIs (without clustering): reporting frequency $\geq 5$ times

AEFI	Times reported
Fatigue	256
Headache	175
Dizziness	105
Myalgia	65
Nausea	48
Syncope	42
Pyrexia	19
Arthralgia	17
Presyncope	15
Malaise	14
Abdominal pain	14
Disturbance in attention	14
Hypersomnia	13
Palpitations	12
Menstrual disorder	9
Influenza like illness	9
Muscular weakness	9
Dyspnoea	8
Pain	8
Migraine	7
Pain in extremity	7
Hypotension	7
Feeling cold	7
Dysmenorrhoea	6
Injection site pain	6
Rash	6
Asthenia	6
Gastrointestinal pain	5
Vision blurred	5
Amenorrhoea	5
Decreased appetite	5
Vertigo	5
Vomiting	5
Dizziness postural	5