



National Institute for Public Health  
and the Environment  
*Ministry of Health, Welfare and Sport*

## **Adverse events following vaccination against human papillomavirus**

*Results of the 2010 campaign in the Netherlands*

RIVM letter report 210012002/2011

T.M. van 't Klooster et al.



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## Colofon

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This investigation has been performed by order and for the account of Ministry of Health, Welfare and Sport and the Inspectorate of Health Care, within the framework of V/210012/11/VO, Safety Surveillance of the National Immunisation Programme, human papillomavirus vaccination.

## Abstract

### **Adverse events following vaccination against human papillomavirus**

Results of the 2010 campaign in the Netherlands

In 2010, less AEs were reported after vaccination against HPV compared with 2009. Furthermore, as in 2009, no unexpected or Serious Adverse Events were reported after vaccination against HPV that were considered causally related to the vaccination.

During 2010, girls born in 1997 were vaccinated against HPV. Furthermore, girls born in 1993-1996, who were not or not fully vaccinated in 2009, were invited again. Intensified surveillance of AEs was performed. Immediate AEs on mass vaccination locations were registered. Spontaneous reports through the enhanced passive surveillance system were collected and a study on the tolerability of the vaccine was performed.

Immediate AEs on locations of mass vaccination occurred in 7.7/10,000 administered doses. Presyncope or syncope was most frequently reported. The reporting rate of spontaneous reports was 5.4/10,000 administered doses overall. The reporting rates of both immediate AEs and spontaneous reports were lower compared with the 2009 campaign. No differences in reporting rates of spontaneous reports were found between the girls born in 1997 (regular NIP) and girls born in 1993-1996 (catch-up campaign). Twenty-three percent of the reports concerned a major AE, including fainting, migraine and convulsions. Of all reports, 67.4% was assessed to be causally related to the vaccination.

In the study on tolerability, at least one questionnaire was returned by 2308 girls (65%). Local reactions were reported in 82.4%, mostly pain at the injection site and/or reduced use of the arm. Of all local reactions, 14.8% was classified as pronounced. In 78.7% any systemic AE was reported, in which myalgia was reported the most often. The reported proportions of local reactions and systemic AEs were lower than in the 2009 campaign. Some local reactions and systemic AEs increasing with age, and most incidences were lower after the second and third dose than after the first dose. The GP was visited by 17 girls (0.4%) within one week after the vaccination, but none visited the hospital.

Results are used to inform public and professionals on the safety profile of the HPV vaccine observed in the period post introduction of mass vaccination.

#### Keywords:

Adverse events following immunisation, safety surveillance, human papillomavirus, HPV vaccination, National Immunisation Programme

## Rapport in het kort

### **Bijwerkingen na vaccinatie tegen humaan papillomavirus**

Resultaten van de 2010 campagne in Nederland

In 2010 werden er minder bijwerkingen gemeld na vaccinatie tegen HPV dan in 2009. Ook zijn er in 2010, net als in 2009, geen onverwachte of volgens de criteria ernstige bijwerkingen (Serious Adverse Events) gemeld die door het vaccin zijn veroorzaakt.

In 2010 zijn meisjes die geboren zijn in 1997 gevaccineerd tegen HPV. Ook zijn meisjes geboren in 1993-1996, die niet (volledig) waren gevaccineerd in 2009, nogmaals uitgenodigd. Tijdens deze campagne is onderzoek gedaan naar de mogelijke bijwerkingen van het vaccin. De mogelijke bijwerkingen die optraden op de vaccinatielocaties werden geregistreerd. Verder werden spontane meldingen in het reguliere systeem voor meldingen van mogelijke bijwerkingen verzameld en is er een onderzoek gedaan naar de verdraagbaarheid van het vaccin.

Verschijnselen die kort na de vaccinatie optraden kwamen 7,7 keer voor per 10.000 toegediende doses. Hierbij kwam (bijna)flauwvallen het meest voor. Spontane meldingen van mogelijke bijwerkingen werden in 5,4 keer per 10.000 toegediende doses gemeld. De meldgraad van zowel verschijnselen die kort na de vaccinatie optraden als van spontane meldingen was lager dan tijdens de campagne in 2009. Bij de spontane meldingen ging het in 23% om een heftige gebeurtenis zoals flauwvallen, migraine en stuipen. Van alle meldingen van mogelijke bijwerkingen van het vaccin werd in 67,4% een oorzakelijk verband met de vaccinatie vastgesteld.

In de studie naar de verdraagbaarheid is door 2308 meisjes (65%) tenminste één vragenlijst teruggestuurd. Een reactie rond de prikplaats werd gerapporteerd door 82,4% van de meisjes, voornamelijk pijn en verminderd gebruik van de arm. Hiervan classificeerde 14,8% van de meisjes de reactie als heftig. Algemene verschijnselen waaronder spierpijn, moeheid of hoofdpijn werd gerapporteerd door 78,7% van de meisjes. Het percentage gerapporteerde lokale reacties en algemene bijwerkingen was lager dan in 2009. Het voorkomen van sommige mogelijke bijwerkingen steeg met de leeftijd en was meestal lager na de tweede en derde dosis dan na de eerste dosis. Zeventien meisjes (0,4%) hebben de huisarts bezocht in de week na de vaccinatie, maar niemand heeft het ziekenhuis bezocht.

De resultaten worden gebruikt om het publiek en de professionals te informeren over het veiligheidsprofiel van het HPV vaccin in de periode na introductie van massa vaccinatie.

Trefwoorden:

Bijwerkingen na vaccinatie, veiligheidsbewaking, humaan papillomavirus, HPV vaccinatie, Rijksvaccinatieprogramma

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## Summary

In 2010, for the first year human papillomavirus (HPV) vaccination was offered to 12-year-old girls (born in 1997). Additionally, the 2009 catch-up campaign for girls born in 1993-1996 was extended in 2010 for girls who were not or not fully vaccinated in 2009. Mass vaccination sessions were organised for the three doses.

Like in 2009, intensified safety surveillance of the vaccine was performed. Firstly, report forms were distributed on all vaccination locations for the recording of immediate adverse events (AEs). Also, spontaneous reports received through the passive surveillance system routinely in place at RIVM were evaluated. Finally, a web-based questionnaire study on the tolerability was performed, in which local and systemic AEs were reported. This report presents the results of the surveillance of AEs following HPV vaccination in 2010.

On 168,134 administered doses of which information was available, we received 130 reports of immediate AEs, resulting in a reporting rate of 7.7/10,000 administered doses. In 97 cases it concerned presyncope or syncope and in 33 cases other vasomotor symptoms. An injury was reported in 10 cases. The ambulance staff, present at the vaccination locations, assisted two girls, and three girls consulted their GP.

In total 237,559 doses were administered in 2010, for which 129 adverse events following immunisation (AEFI) were reported to the enhanced passive surveillance system. The overall reporting rate was 5.4/10,000 administered doses, and was similar for girls born in 1997 (regular NIP) and girls born in 1993-1996 (catch-up campaign). In 77% of the cases it concerned a minor event, of which 64% was considered to be causally related to the vaccination. A major event concerned 23% of the spontaneous reports, in which 80% was assessed to be causally related with the vaccination. In 62% the reports were classified as general illness, mostly minor, and in 16% local reactions were predominant. Medication was used in 19%, the GP consultation rate and the hospital consultation rate were 1.5/10,000 administered doses and 0.5/10,000 administered doses, respectively.

In the study on tolerability, 3552 questionnaires were e-mailed after each dose. At least one questionnaire was returned by 4501 girls (42%), of which 1556 concerned the regular NIP and 751 the catch-up campaign. Local reactions were reported in 88% after the first dose, in 80% after the second dose, and in 79% after the third dose. Pain at the injection site and reduced use of the arm were the most often reported. Following the three successive doses 17%, 13%, and 15% of the local reactions were classified as pronounced. For pain and swelling, the incidence increased with age. Furthermore, pain, reduced use of the arm, and swelling were dose dependent.

Any systemic AE was reported following the three successive doses in 86%, 75%, and 76%, respectively. Myalgia was the most often reported systemic AE (73%). The incidence of some systemic AEs increased with the age of the girl. Also, after the second and third dose lower proportions were reported than after the first dose for almost all systemic AEs.

Overall, 10.3% used analgesics after the vaccination and 17 girls (0.4%) visited a GP within one week after administering the vaccine. None of the girls visited the hospital.

In 2010, less AEs were reported after vaccination against HPV compared with the catch-up campaign in 2009. The reporting rate of both immediate AEs as well as spontaneous reports were in 2010 lower than in 2009. Also, the reporting rate of presyncope and syncope was in 2010 lower than in 2009. However, the proportion of causally related spontaneous reported AEFI has increased compared with the 2009 HPV campaign. In the study on tolerability performed in 2010, girls reported lower proportions of local reactions, especially pronounced reactions, and systemic AEs than in a same study in 2009. The same trends for age and dose were observed in the reporting of AEs as in 2009. Explanations for the decrease in the reporting of AEs is the fact that in 2010 younger girls were vaccinated (mainly 12-year-olds) than in 2009 (13-16-year olds), and the increased adverse publicity in 2009 has declined in 2010. Overall in 2010, no serious AEs with assessed causality to the vaccination were reported.

These post-marketing results are used to inform health care professionals and the public to help increase the confidence in the safety of HPV vaccination and vaccination in general.



## 1 Introduction

Since 2010, vaccination against human papillomavirus (HPV) is included in the National Immunisation Programme (NIP) and is offered each year to 12-year-old girls. Older girls, 13-16 years of age (birth cohorts 1993 to 1996), got the opportunity to receive HPV vaccination in a catch-up campaign in 2009.<sup>1</sup> The compliance with this 2009 catch-up campaign was low (45% of the invited girls completed the vaccination schedule in 2009). Therefore, girls born in 1993 to 1996 who were not or not fully vaccinated again received another invitation for HPV vaccination in 2010.<sup>2</sup>

HPV vaccination was given during mass vaccination campaigns, organised by the Municipal Health Services (MHS). The bivalent HPV vaccine was used in a three dose schedule at 0, 1, and 6 months. The doses were given in spring and autumn.

During the first HPV vaccination campaign in 2009 the Centre for Infectious Disease Control (CIb) of the National Institute for Public Health and the Environment (RIVM) performed an intensified safety surveillance, because it concerned the introduction of a new vaccine as well as a new target group in the NIP.<sup>3</sup> Safety surveillance is necessary to verify the safety profile observed in clinical trials. Furthermore, the occurrence of adverse events (AEs) could be a reason for vaccine refusal. Therefore, it is important that girls and their parents have correct information and expectations, which could help increase the confidence in vaccination. In 2009, reporting rates of AEs were high, especially after the first dose. However, through three different surveillance tools, no rare or severe AEs causally related to the vaccination were detected.<sup>3</sup>

In 2010, the safety surveillance was continued because this year was the first year of the regular vaccination of 12-year-old girls in the NIP. In addition, the catch-up campaign was extended. As in 2009, the safety surveillance in 2010 consisted of three different surveillance tools: immediate AEs at vaccination sites, enhanced passive surveillance and a questionnaire survey on tolerability. The results of this safety surveillance in 2010 are presented in this letter report. Chapter 2 describe the immediate AEs at mass vaccination sites. Chapter 3 presents reports of adverse events of the enhanced passive surveillance. In Chapter 4 the study on tolerability is presented. Finally, Chapter 5 gives an overall conclusion on the safety results for HPV vaccination in 2010.

## 2 Immediate adverse events on vaccination sites

### 2.1 Methods

For the monitoring of immediate AEs during mass vaccination sessions report forms were distributed among all mass vaccination sites. The MHS personnel were asked to fill in these report forms and send them to the RIVM.

Two separate forms were distributed. One form was designed for registration of each immediate AE individually, containing information on the patient, symptoms together with time interval and duration, injury and medical intervention. The other form was for collection of aggregated information, i.e. the total number of AEs on the vaccination site together with the total number of administered vaccines during the vaccination session and a description of the local circumstances.

Reporting rates with 95% confidence intervals (CI) were calculated after all three doses. Presyncope was defined as pallor in combination with one additional symptom like dizziness, sweating, nausea, vomiting, or jerks. Or, when pallor was not reported, three symptoms out of the preceding list needed to be present. Furthermore, injury and medical intervention were gathered.

### 2.2 Results

#### 2.2.1 Number of reports

In 2010, nearly 70% of the girls eligible for HPV vaccination was born in 1997 (regular NIP). Girls born in 1993-1996 (catch-up campaign) accounted for about 30% for all invited girls.

For the registration of immediate AEs, information was available on 168,134 doses, which is 74% of all administered doses. We received 130 reports of immediate AEs, resulting in a reporting rate of 7.7 per 10,000 administered doses. For absolute numbers of reports by birth cohort per dose see Table 2.1 and for reporting rates by event per dose see Table 2.2.

*Table 2.1 Absolute numbers of reported immediate AEs by birth cohort and per dose*

Event	Absolute number of AEs				
	1 <sup>st</sup> dose	2 <sup>nd</sup> dose	3 <sup>rd</sup> dose	Unknown	All doses
1993	0	1	2	0	<b>3</b>
1994	4	0	1	0	<b>5</b>
1995	4	1	1	0	<b>6</b>
1996	9	2	0	0	<b>11</b>
1997	42	13	9	0	<b>64</b>
Unknown	18	11	6	6	<b>41</b>
<b>Total</b>	<b>77</b>	<b>28</b>	<b>19</b>	<b>6</b>	<b>130</b>

*Table 2.2 Reporting rates of immediate AEs and medical intervention per 10,000 vaccinated girls*

Event	Incidence rate per 10,000 administered doses (95% CI)			
	1 <sup>st</sup> dose	2 <sup>nd</sup> dose	3 <sup>rd</sup> dose	All doses
Presyncope and syncope	7.8 (5.8-9.8)	4.0 (2.2-5.7)	3.1 (1.4-4.7)	5.8 (4.6-6.9)
Other vasomotor symptoms	2.1 (1.1-3.1)	1.9 (0.7-3.1)	1.4 (0.3-2.6)	2.0 (1.3-2.6)
Jerking	0.3 (0-0.6)	0.4 (0-1.0)	0.2 (0-0.7)	0.3 (0-0.6)
Vomiting	0.1 (0-0.4)	0.2 (0-0.6)	-	0.1 (0-0.3)
Dyspnoea	0.3 (0-0.6)	-	0.2 (0-0.7)	0.2 (0-0.4)
Skin symptoms	0.1 (0-0.4)	-	-	0.1 (0-0.3)
<b>Total</b>	<b>9.9 (7.7-12.1)</b>	<b>5.8 (3.7-8.0)</b>	<b>4.5 (2.5-6.5)</b>	<b>7.7 (6.4-9.1)</b>
Consultation of GP	0.1 (0-0.4)	-	0.5 (0-1.1)	0.2 (0-0.3)
Assistance from ambulance staff	0.1 (0-0.4)	0.2 (0-0.6)	-	0.1 (0-0.3)

#### 2.2.2 *Presyncope and syncope*

The most reported immediate AE with 97 reports in total was presyncope or syncope, resulting in a reporting rate of 5.8 per 10,000 administered doses. Jerking (n=5) and vomiting (n=2) only occurred in relation to presyncope or syncope.

#### 2.2.3 *Other vasomotor symptoms*

Other vasomotor symptoms were reported by 33 girls (reporting rate 2.0 per 10,000 administered doses).

#### 2.2.4 *Rash and itchiness*

Only one girl reported skin symptoms (reporting rate 0.1 per 10,000 administered doses). This girl suffered from presyncope also.

#### 2.2.5 *Dyspnoea*

Three times dyspnoea was reported, none of them coinciding with skin symptoms. In all of these cases presyncope or syncope was reported together with the dyspnoea.

#### 2.2.6 *Anaphylactic shock*

No anaphylactic shock was reported.

#### 2.2.7 *Injury and medical intervention*

Injury, such as a wound or bump was reported 10 times, all in relation with syncope. Three girls consulted the general practitioner (GP) of whom one with injury. Two girls were seen by ambulance staff, routinely present at the mass vaccination sites. One of these girls had an injury. Table 2.2 shows the reporting rates of medical interventions per dose.

## 2.3 Discussion

The reporting rate of immediate AEs was lower than in the catch-up campaign in 2009.<sup>3</sup> In 2009 there was much adverse media attention, especially focussed on the safety of the HPV vaccine. This media attention and the fact that it concerned a newly introduced vaccine may have increased the willingness to report AEs.

The absolute number of reported immediate AEs was higher for girls, born in 1997 compared with girls from the cohorts 1993-1996. This may be explained by the fact that 70% of the girls, eligible for HPV vaccination in 2010, originated from the 1997 birth cohort. Unfortunately, we have no cohort specific denominators to calculate reporting rates per cohort. HPV vaccination coverage for girls, born in 1997 was comparable with the coverage of girls, born in 1993-1996 for 2009 and 2010.<sup>4</sup>

In 2010, the reporting rate of presyncope and syncope (5.8/10,000 doses) was also lower than the corresponding reporting rate in the 2009 HPV vaccination campaign (16.8/10,000)<sup>3</sup> and in the 2002 mass vaccination campaign against Meningococcal serotype C (MenC) disease ( 21.4/10,000 for 6-14 year olds and 18.9/10,000 for 15-19 year olds).<sup>5</sup> It is well known that the rate of fainting can vary considerably, depending on environmental factors, prevention efforts and mass reactions.<sup>6</sup>

Like in 2009, again we did not receive any reports of anaphylaxis, causally related to the vaccination. This could be expected in view of the estimated incidence rate between 1 and 10 per 1,000,000 doses reported in literature, and only nearly 240,000 doses administered in 2010.

The surveillance of immediate AEs following HPV vaccination did not cover the entire vaccinated population. Therefore, our results could be an underestimation because of missing reports. On the other hand, it is more likely that information on mass vaccination sessions where no immediate AEs occurred was not sent to RIVM, resulting in an overestimation.

Reporting rates for consultation of a GP or hospital facility (emergency room, outpatient clinic or overnight stay) were low following the 2010 HPV campaign and comparable with the rates found in the 2009 HPV campaign and in the MenC vaccination campaign. Therefore we can conclude that the medical impact of immediate AEs was low. However, it is very important to have such a surveillance system in place at the start of mass vaccination sessions for vaccines newly introduced in the NIP, to monitor these events accurately and thereby hopefully prevent negative impact on the willingness to vaccinate due to rare and/or alleged side effects.<sup>7</sup>

### 3 Enhanced passive surveillance

#### 3.1 Methods

An enhanced passive surveillance system was in place at RIVM from 1962 till 2011. The reporting rates were stable and high, and reporting criteria were well known to all professionals involved in the NIP (Diagram 3.1).<sup>8, 9</sup> The reporting criteria were wide to get a better signal detection, and reporting possibilities were various. AEFI could be reported through the telephone service for consultation and advice for health care professionals. In case of reporting by telephone, a special report form was filled in by the medical expert, answering the phone. Also, special report forms for written notifications could be downloaded from the website and be posted to RIVM. Digital reporting was possible also, as well as reporting by email and through discharge letter.

Undesirable phenomena after vaccination are not necessarily caused by the vaccination. For that reason the neutral term adverse event (AE) or Adverse Event Following Immunisation (AEFI) is used, irrespective of whether or not there is a causal relation between vaccination and the event.

*Diagram 3.1 Reporting criteria for AEs under the HPV vaccination campaign*

- Serious events
- Uncommon events
- Symptoms affecting subsequent vaccinations
- Symptoms leading to public anxiety or concern

***Irrespective of the causal relation***

After verification and completion of data, a (working) diagnosis was made (Diagram 3.2). If symptoms do not fulfil the criteria for a specific diagnosis, the working diagnosis was made based on the most important symptoms. Case definitions were used for the most common AEFI and current medical standards were used for other diagnoses. Some categories are subdivided in minor and major according to the severity of symptoms. Major is not the same as medically serious or severe, but this group does contain the severe events.

Diagram 3.2 Diagnoses of AEFI, especially designed for the NIP

Local (inflammatory) symptoms	If accompanying systemic symptoms do not prevail.	
	<i>minor</i>	(Atypical) symptoms, limited in size and/or duration.
	<i>major</i>	Extensive and/or prolonged and include abscess or erysipelas.
General illness	Includes all events that cannot be categorised elsewhere (symptoms as part of another event or syndrome were not booked here separately).	
	<i>minor</i>	Symptoms like crying < 3 hours, fever < 40.5 °C, irritability, pallor, feeding/eating and sleeping problems, mild infections, etcetera.
	<i>major</i>	Symptoms like fever ≥ 40.5 °C, autism, diabetes, idiopathic thrombocytopenic purpura (ITP), severe infections, etcetera.
Persistent screaming	<i>(major)</i>	(Sudden) screaming, non-consolable and lasting for three hours or more (symptoms as part of another event or syndrome were not booked here separately).
General skin symptoms	Symptoms that were not a part of general (rash) illness and not restricted to the reaction site.	
	<i>minor</i>	According to severity.
	<i>major</i>	According to severity.
Discoloured legs or arms	<i>(major)</i>	Even or patchy discoloration of the leg(s)/arm(s) and/or leg/arm petechiae, with or without swelling (extensive local reactions were not included).
Faints	Symptoms were not explicable as post-ictal state or part of another disease entity.	
	<i>(major)</i>	<ul style="list-style-type: none"> <li>- Collapse: sudden pallor, loss of muscle tone and consciousness, also called Hypotonic Hyporesponsive Episode.</li> <li>- Breath holding spell: fierce crying, followed by breath holding and accompanied with no or just a short period of pallor/cyanosis.</li> <li>- Fainting: sudden onset of pallor, sometimes with limpness and accompanied by vasomotor symptoms.</li> </ul>
Fits	<i>(major)</i>	<ul style="list-style-type: none"> <li>- Convulsions: discriminated in non-febrile and febrile convulsions and include all episodes with tonic and/or clonic muscle spasms and loss of consciousness. Simple febrile seizures last ≤ 15 minutes. Complex febrile seizures last &gt; 15 minutes recur within 24 hours or have asymmetrical spasms.</li> <li>- Epilepsy: definite epileptic fits or epilepsy.</li> <li>- Atypical attack: paroxysmal occurrence, not fully meeting criteria for collapse or convulsion.</li> </ul>
Encephalitis / encephalopathy	<i>(major)</i>	A child < 24 months with encephalopathy has loss of consciousness for ≥ 24 hours. Children > 24 months have at least two out of three criteria: change in mental state, decrease in consciousness, seizures. In case of encephalitis symptoms were accompanied by inflammatory signs. Symptoms were not explained as post-ictal state or intoxication.
Anaphylactic shock	<i>(major)</i>	Circulatory insufficiency with hypotension and life threatening hypoperfusion of vital organs with or without laryngeal oedema or bronchospasm.
Death	<i>(major)</i>	Any death following immunisation (preceding diseases or underlying disorders were not booked separately).

Causal relation would then be appraised on the basis of a checklist, resulting in an indication of the probability/likelihood that the vaccine is indeed the cause of the event. This list is not (to be) used as an algorithm although there are rules and limits for each point of consideration (Diagram 3.3). Causality was classified by one of five different categories.

*Diagram 3.3 Criteria for causality categorisation of AEFI*

1-Certain	Involvement of vaccine/vaccination is conclusive through laboratory proof or mono-specificity of the symptoms and a proper time interval.
2-Probable	Involvement of vaccine is acceptable with high biologic plausibility and fitting interval without indication of other causes.
3-Possible	Involvement of vaccine is conceivable, because of the interval and the biologic plausibility but other cause are as well plausible/possible.
4-Improbable	Other causes are established or plausible with the given interval and diagnosis.
5-Unclassifiable	The data are insufficient for diagnosis and/or causality assessment.

An expert panel re-evaluates selected formal written assessments by the RIVM on diagnosis and causality. This panel consists of specialists on paediatrics, neurology, immunology, vaccinology, pharmacovigilance, microbiology, and epidemiology.

All notifications were coded in a predefined uniform way and reporting rates were calculated. The denominator was available from the national immunisation registry.<sup>10, 11</sup>

## 3.2 Results

### 3.2.1 Number of administered doses and number of reports

In 2010, a total of 237,559 doses were administered, of which 164,385 in the regular NIP and 73,174 in the catch-up campaign. Of the 12-year old girls in the regular NIP, 58,751 (61.4%) received a first dose, 55,976 (58.5%) also received a second dose, and 49,658 (51.9%) also a third dose. In the 2010 catch-up campaign, a first dose was administered to 25,320 girls, a second dose to 23,477 girls, and a third dose to 24,377 girls. Overall, in the 2009 and 2010 catch-up campaign, 52.2% of the birth cohorts 1993-1996 are fully vaccinated against HPV.

Until 1 January 2011 we received 129 reports of AEFI during the mass vaccination against HPV in 2010. Of these reports, 69% (n=89) concerned girls born in 1997, receiving an HPV vaccination through the regular NIP. In 31% (n=40) 13-16 year old girls, who received the vaccination in the catch-up campaign, were involved.

More than half of the reports (n=67; 52%) followed administration of the first dose, 22% and 26% of the reports concerned the second and third dose, respectively. See Figure 3.1 for reports per week during the entire campaign.

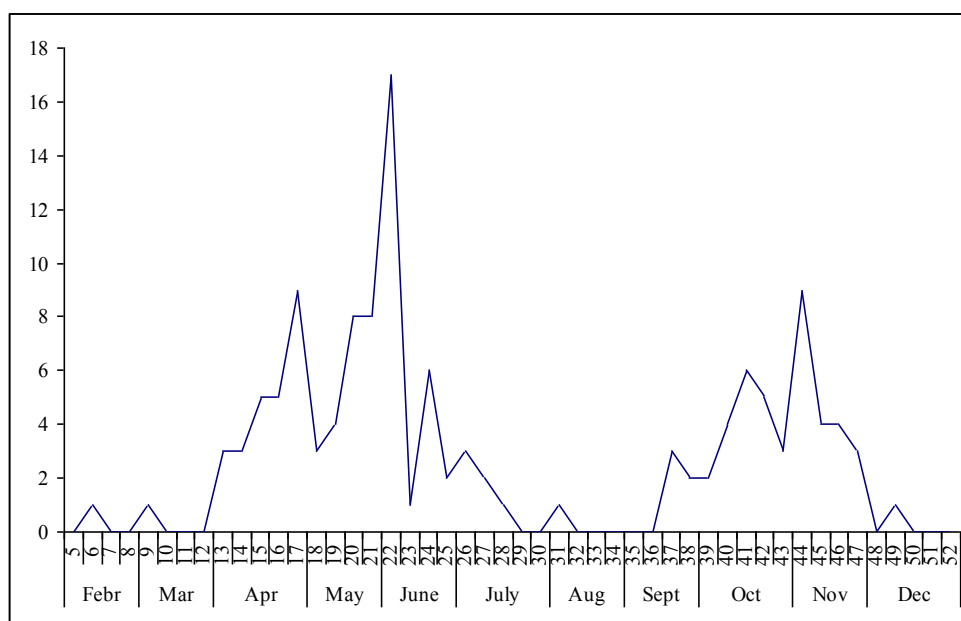


Figure 3.1 Number of reports per week following HPV vaccination during 2010

Professionals of the MHS departments accounted for 61% (n=79) of the reports. Parents were the reporter in 33% (n=43) of the cases. Other reports were sent in by GPs (1%), paediatricians (1%) and others (2%).

Absolute numbers of reports must be seen in relation to the number of vaccinated girls. During 2010, 237,559 HPV doses were administered. Therefore, the overall reporting rate was 5.4 per 10,000 administered doses (95% CI 5.4-6.4). As already reported, the absolute number of reports differed per birth cohort. However, reporting rates for 12-year-old girls (regular NIP) and 13-16-year-old girls (catch-up campaign) were more or less equal (Figure 3.2).

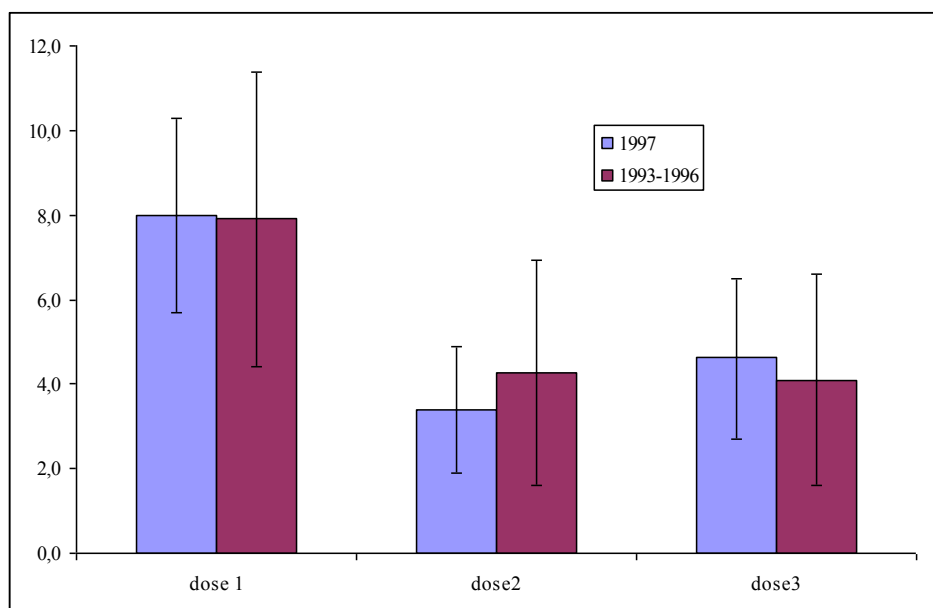


Figure 3.2 Dose specific reporting rates following HPV vaccination in 2010 for cohort 1997 and cohort 1993-1996



### 3.2.2 Severity of reported adverse events and medical intervention

The severity of reported AEs is historically categorised in minor and major events (see section 3.1). The number of major and minor events were 30 (23%) and 99 (77%), respectively.

The level of medical intervention may also illustrate the impact of AEs. In 17.1% (n=22) of the reports no medical help was sought or was not recorded to us. Paracetamol or other home medication was administered in 18.6% (n=24). In 27.9% (n=36) a GP was contacted, resulting in a contact rate of 1.5 per 10,000 administered doses. In 9.3% (n=12) of the reports, girls went to a hospital, giving a consultation rate of 0.5 per 10,000 (Table 3.1).

*Table 3.1 Intervention and reported AEFI following HPV vaccination in 2010 (irrespective of causality)*

Event	Intervention										Total
	None	Suppositories <sup>a</sup>	Municipal Health clinic <sup>b</sup>	GP by telephone <sup>c</sup>	GP <sup>d</sup>	Ambulance <sup>e</sup>	Out-patient	Emergency care	Hospital admission	Unknown	
Local reaction	4	1	9	1	1	-	1	-	-	2	19
General minor illness	12	20	16	8	12	-	3	1	-	3	75
General major illness	-	-	1	1	-	-	2	-	1	-	5
Skin symptoms	-	-	-	3	4	-	-	-	-	-	7
Faints	1	3	9	1	2	-	-	2	-	-	18
Fits	-	-	-	-	1	-	1	-	-	-	2
Discoloured arms	-	-	1	-	2	-	-	-	-	-	3
Anaphylactic shock	-	-	-	-	-	-	-	-	-	-	-
Encephalopathy/encephalitis	-	-	-	-	-	-	-	-	-	-	-
Death	-	-	-	-	-	-	-	-	-	-	-
<b>Total</b>	<b>17</b>	<b>24</b>	<b>36</b>	<b>14</b>	<b>22</b>	<b>-</b>	<b>7</b>	<b>3</b>	<b>1</b>	<b>5</b>	<b>129</b>

<sup>a</sup>paracetamol suppositories, stesolid rectioles and other (previously) prescribed or over the counter drugs are included.

<sup>b</sup>telephone call or special visit to the clinic.

<sup>c</sup>consultation of general practitioner by telephone.

<sup>d</sup>examination by general practitioner.

<sup>e</sup>ambulance call and home visit without subsequent transport to hospital.

### 3.2.3 Causal relation

Events with (likelihood of) causality assessed as certain, probable or possible were considered as adverse reactions (AR) (see section 3.1). In 2010 following HPV vaccination, 67.4% (n=87) of reports were ARs. For major events only, 80.0% (n=24) were regarded as AR, while 63.6% (n=63) of the minor AEs was considered to be an AR. Percentages of causally related reports per dose were more or less equal. However, absolute numbers are small. There were great differences in causality between the different event categories (Table 3.2).

*Table 3.2 Causality of reported AEFI following HPV vaccination in 2010*

Event		Causality			Total	% AR*
		Certain Probable Possible	Improbable	Non classifiable		
Local reaction		19	0	-	19	100
General illness	minor	44	31	-	75	59
	major	2	3	-	5	40
Skin symptoms		2	5	-	7	29
Faints		17	1	-	18	94
Fits		0	2	-	2	0
Discoloured arms		3	0	-	3	100
Anaphylactic shock		-	-	-	-	-
Encephalopathy/ encephalitis		-	-	-	-	-
Death		-	-	-	-	-
<b>Total</b>		<b>87</b>	<b>42</b>	<b>-</b>	<b>129</b>	<b>67</b>

\*Percentage of reports considered adverse reactions (causality certain, probable, possible) excluding non-classifiable events.

### 3.2.4 Expert panel

In relation to the HPV vaccination campaign in 2010, the expert panel reassessed 2 reports (1.6%). The expert panel agreed in both cases with the (working) diagnosis and causality assessment, determined by RIVM.

### 3.2.5 Local reactions

Local reactions were predominant in 16% of the reports (n=19). Three of the reported local reactions were classified as major because of size, severity, duration or intensity. In all but three reports inflammation was the most prevalent aspect.

### 3.2.6 Minor general illness

Events that were not classifiable in any of the specific event categories are listed under general illness, depending on severity subdivided in 'minor' or 'major' (see section 3.1). In 75 girls the event was considered to be minor general illness. Only in a very few times a definite diagnosis was possible; mostly working diagnoses were used (Table 3.3). In 45% (n=34) the working diagnosis was fever, in all but one report considered as causally related to the vaccination.

*Table 3.3 Main (working) diagnosis or symptom in category of minor general illness of reported AEFI following HPV vaccination in 2010*

Symptom or diagnosis	Number	AR*
Fever	34	33
Gastro-intestinal tract disorders, including infections	10	1
Headache	7	5
Menstruation problems	4	0
Fatigue	4	1
Airway and lung disorders, including infections	4	1
Infection	2	0
Shivering	2	2
Other	8	1
<b>Total</b>	<b>75</b>	<b>44</b>

\*Number of considered adverse reactions.

### 3.2.7 *Major general illness*

Five times the reported AEs were categorised as major general illness. Two times a causal relation with the vaccination was assessed, once in a report of fever  $\geq 40.5^{\circ}\text{C}$ , once in a report of complicated migraine. In the other three reports a causal relation with the vaccination was considered unlikely. These reports considered a viral disease, pyelonephritis and a neurological disorder.

### 3.2.8 *General skin symptoms*

Skin problems were the main or only feature in seven reports. Four of these reports considered exanthema (twice causally related), in two reports the girl suffered from urticaria (none with assessed causality). The remaining report considered swelling of the armpit of the other arm (not causally related).

### 3.2.9 *Faints*

Through the enhanced passive surveillance system we received 18 reports of presyncope or syncope, of which only one was considered to be a chance occurrence. However, most reports on presyncope and syncope were received through our surveillance of immediate AEs, which is discussed in the previous section.

### 3.2.10 *Fits*

During the 2010 HPV campaign, one girl with epilepsy was reported and one girl had a non-febrile atypical attack. In both reports a causal relation with the vaccination was considered unlikely because of the lag time.

### 3.2.11 *Discoloured arms*

Discolouration of (part of) the arm in which the vaccination was administered, was reported three times. The eyewitness account from parents or the girl herself showed that these events resemble the discoloured legs syndrome, as described by Kemmeren et al., mainly occurring in infants.<sup>12</sup> A causal relation with the vaccination was assessed in all three reports.

## 3.3 **Discussion**

In 2010, the reporting rate of spontaneous reports following HPV vaccination was much lower compared with the 2009 HPV vaccination campaign. This may be influenced by the increased adverse publicity, focussed on safety, during the 2009 HPV vaccination campaign or because it concerned the introduction of a new vaccine in 2009. The reporting rate in 2010 is comparable with the rate of spontaneous reports after the 2002 MenC vaccination campaign.<sup>9, 13</sup>

The reporting rate following the first dose was higher than the rate of the second and third dose. We found no information on dose specific reporting rates in literature. Whether this is a real effect or due to difference in underreporting is not clear. With consecutive doses, professionals routinely ask for AEs after the preceding vaccination before administering the next dose. This may explain the highest rate after the first dose. The relative long interval between the second and third dose may have influenced the memory of some girls, resulting in a slightly lower rate after the second dose compared with the third dose. Continued monitoring the reporting rate after the HPV vaccination is important. A (selective) decreasing willingness to report hampers a fast signal detection of rare AEFI. Despite their limitations, passive surveillance systems are an important tool for signal detection, the reports being input for observed versus expected analysis both nationally and internationally.<sup>14</sup>

The proportion of causally related AEFI has increased compared with the 2009 HPV campaign. The same applies for the proportion of major AEFI and the reports of major events with assessed causality during the 2010 HPV campaign. This may be explained by the fact that professionals and public have more knowledge on true and perceived side effects of the HPV vaccine and therefore more often report AEFI with a plausible association with the HPV vaccine. On the other hand, peculiar events can and always will occur in close time relation with vaccination just by chance. Reporting coincidental events following vaccination indicates good willingness to report. Therefore, a further increasing percentage of causally related AEFI can also indicate a decline in reporting behaviour and therefore increased underreporting. The percentage of causally related reports per dose did not change significantly. Therefore, dose dependency had minor influence. However, absolute numbers are small.

The proportion of reports with predominantly local symptoms and the percentage of reports categorised as minor general illness were comparable with 2009 and together accounted for 74% of all reports. However, the contribution of each category to the total number of reports after HPV vaccination differs from the distribution of the categories in the reports following the NIP as a whole. Most reports after NIP vaccination are related to infant vaccinations and AEFI are clearly age dependent. For instance collapse and febrile convulsions often occur after the first vaccinations and around one year of age following the vaccinations at 11 and 14 months of age, respectively. This influences the safety profiles of the vaccines used and therefore has impact on the distribution of the categories of reported AEFI. Continued enhanced surveillance of spontaneous reports after HPV vaccination is important to increase our knowledge of the safety profile of the HPV vaccine, and to detect changes and trends in AEFI over the time.

The 129 spontaneous reports following bivalent HPV vaccine revealed no new, rare AEFI.

Equal to the 2009 HPV campaign we received some reports on menstruation problems, a symptom, often occurring in these age group and obviously not related to the vaccination.

Furthermore, one report of complicated migraine was received compared with 5 in 2009. We currently are assessing the age- and sex- specific background rates of this disorder and plan a data linkage study to investigate the possible association between migraine and HPV vaccination.

Also three 'discoloured leg syndromes', however located in the arm, were reported compared with four corresponding reports in 2009. Further studies are needed to gain more insight in this syndrome.<sup>12</sup>

## 4 Tolerability

### 4.1 Methods

The study on tolerability was performed at six mass vaccination sites in the centre of the Netherlands. Over 3000 girls, comprising at least 1500 from the regular NIP (born in 1997) and at least 1500 from the catch-up campaign (born in 1993-1996), were approached during the first vaccination session. They were asked to fill in a Web-based questionnaire to measure frequent AEs. A week after each of the three doses they received the link to the questionnaire by e-mail.

The questionnaire contained questions about date of birth, date and location of vaccination, underlying illness (eczema, allergy, asthma, hay fever, and diabetes mellitus), illness during the week before vaccination (headache, cold, or flu) or at the time of vaccination (cold or flu), and the occurrence of AEs within 7 days after immunisation. Girls were asked to record local reactions (swelling, redness, pain at the injection site, swelling in armpit or reduced use of the arm) and systemic events (fever, listlessness, crying, cold, coughing, dyspnoea, fatigue, sleeping problems, nausea, vomiting, diarrhoea, abdominal pain, headache, dizziness, fainting, myalgia, joint pain, muscle contractions, sweating, rash, itch or other unsolicited symptoms). The severity of local reactions was graded on a four-point scale, for swelling and redness: none, less than 2.5 cm (comparable to the size of a 2-Euro coin), 2.5 to 5 cm and more than 5 cm, and for pain at the injection site, swelling in armpit and reduced use of the arm: none, mild, moderate or pronounced. Fever was reported on a continuous scale, but in this report presented as  $\geq 38^{\circ}\text{C}$ .<sup>15</sup> Other systemic events were dichotomised (yes/no). In addition, time interval and duration of symptoms were collected, as well as the use of analgesics, other medical intervention, absence from school, sport or other activities, or a parent's or guardian's absence from work.

During 2010, an additional questionnaire was developed for measuring the occurrence of symptoms (fever, listlessness, crying, cold, coughing, flu, dyspnoea, fatigue, sleeping problems, nausea, vomiting, diarrhoea, abdominal pain, headache, dizziness, fainting, myalgia, joint pain, muscle contractions, sweating, rash, itch or other unsolicited symptoms), absence, and medical interventions without vaccination. At the time of the vaccination in autumn, girls were also asked to report symptoms that occurred in the week before the third vaccination. A link to this questionnaire was sent somewhere around the vaccination date by e-mail.

The incidence of local reactions and systemic AEs was calculated for each of the three doses with corresponding 95% confidence intervals (CI) and median duration. Also, frequencies of underlying illness, sickness during the week before or at the time of vaccination, the use of analgesics, other medical intervention and absence were analysed with 95% CI and median duration if applicable. Differences in age and between doses were analysed by using generalized linear mixed models (GLMM). In addition, we analysed differences between the regular NIP (girls born in 1997) and the catch-up campaign (girls born in 1993-1996), including girls who already started with vaccination in 2009 and girls who started with vaccination in 2010 ('late adopters').

## 4.2 Results

### 4.2.1 Response and participants

A total of 10,656 questionnaires were e-mailed, 3552 after each vaccination. Overall, 2308 girls (65%) participated in the study, which returned together 4501 questionnaires (Figure 4.1). All three questionnaires were returned by 752 (21%) participants (Table 4.1).

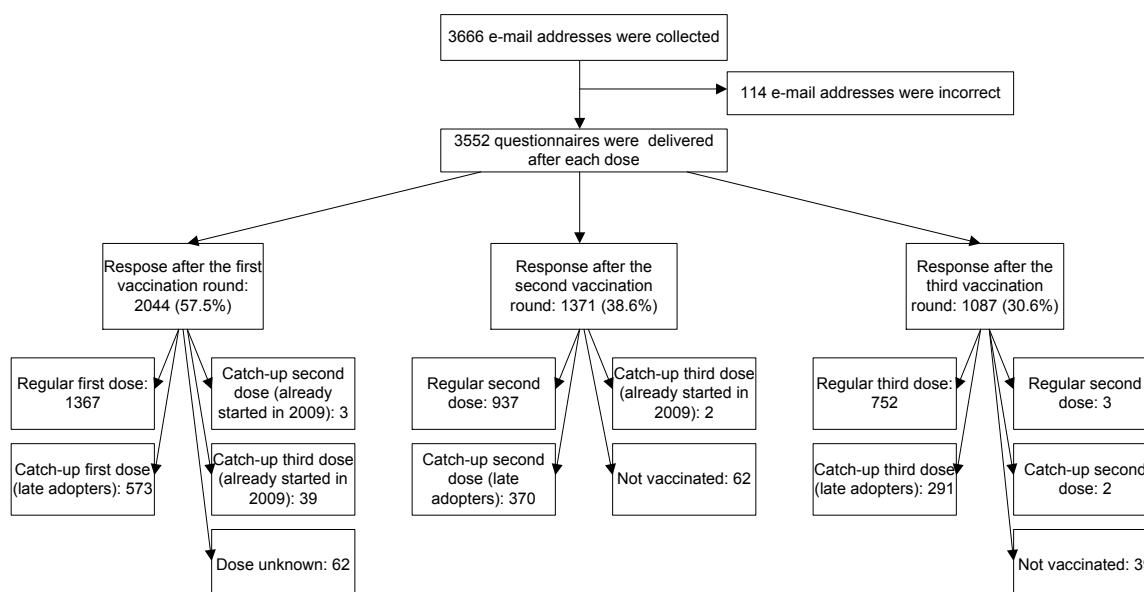


Figure 4.1 Response after each vaccination round

Of the participants, 1557 (67%) were vaccinated under the regular NIP and 751 (33%) under the catch-up campaign. Most of the participants of the catch-up campaign were late adopters (Table 4.1).

Table 4.1 Participants by dose

Birth cohort	1 <sup>st</sup> dose (n)	2 <sup>nd</sup> dose (n)	3 <sup>rd</sup> dose (n)	Complete responders (n)	Started in 2009 (catch-up) <sup>1</sup> (n)	Late adopters (catch-up) <sup>1</sup> (n)
1993 (n=133)	104	58	59	37	14	104
1994 (n=163)	129	75	61	39	14	129
1995 (n=190)	143	100	80	44	20	143
1996 (n=265)	197	142	132	79	31	197
1997 (n=1557)	1367	940	752	553	NA	NA
Total (n=2308; 65.0%)	1940 (54.6%)	1315 (37.0%)	1084 (30.5%)	752 (21.2%)	79 (10.5%)	573 (76.3%)

NA = not applicable.

<sup>1</sup>For 99 girls who were vaccinated under the catch-up campaign it is unknown if they were already started with the vaccinations in 2009 or if they were late adopters.

### 4.2.2 Local reactions

Of all girls, 88.5% (95% CI 86.9-89.8) reported a local reaction at the vaccination site after the first dose, 79.5% (95% CI 77.2-81.7) after the second dose, and 79.2% (95% CI 76.7-81.6) after the third dose. The reported local reactions included mostly pain at the injection site (75%) and/or reduced use of the arm (56%; Figure 4.1). More local reactions were reported by girls with a headache, cold or flu during the week before vaccination and/or cold or flu at

the time of vaccination (OR 1.6; 95% CI 1.2-2.2, and 2.0; 95% CI 1.6-2.6, respectively).

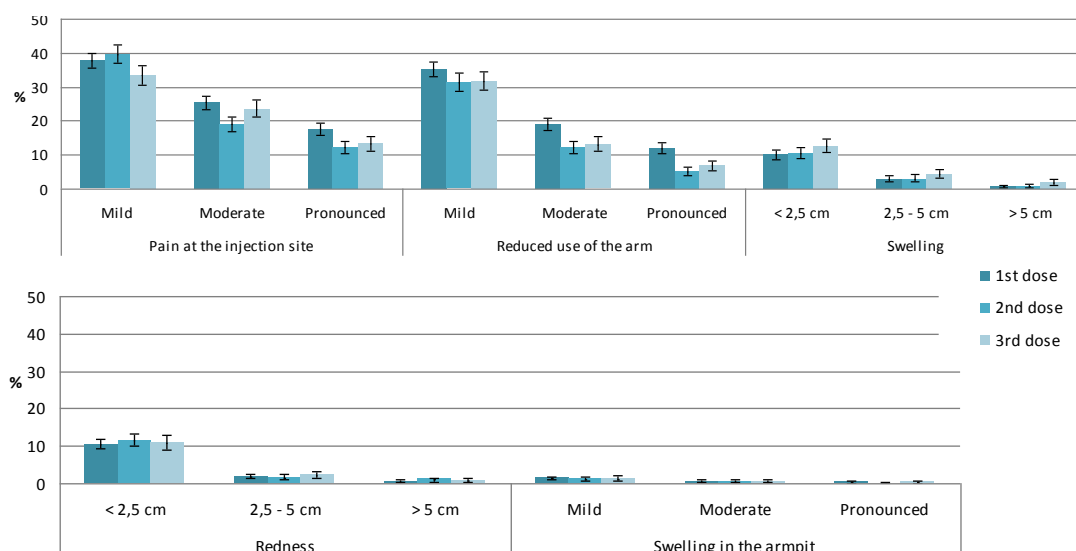


Figure 4.1: Incidence proportions of local reactions by severity and dose, for cohorts 1993-1997

Reported local reactions were classified in three grades of severity. In 17.2%, 12.6%, and 14.5%, respectively after the three successive doses, the local reactions were classified by the girl as pronounced. The median duration of the local reactions ranged between 35 and 130 hours and increased with an increasing severity of the reaction (Table 4.2). Almost all reactions at the injection site started within 72 hours, indicating a relation to the vaccination (Table 4.2).

Table 4.2 Number and percentage of reported local reactions with median duration and proportion within 72 hours after vaccination by dose, for cohorts 1993-1997

Local reaction	1 <sup>st</sup> dose			2 <sup>nd</sup> dose			3 <sup>rd</sup> dose		
	N (%)	Median duration (hrs)	Start within 72 hrs (%)	N (%)	Median duration (hrs)	Start within 72 hrs (%)	N (%)	Median duration (hrs)	Start within 72 hrs (%)
<b>Pain</b>									
Mild	730 (37.6)	47	98	520 (39.5)	44	97	362 (33.4)	45	98
Moderate	492 (25.4)	66	99	250 (19.0)	60	99	255 (23.5)	70	97
Pronounced	343 (17.7)	84	99	159 (12.1)	89	98	144 (13.3)	96	98
<b>Reduced use of the arm</b>									
Mild	685 (35.3)	43	97	413 (31.4)	38	95	345 (31.8)	43	96
Moderate	367 (18.9)	54	98	162 (12.3)	53	97	142 (13.1)	61	97
Pronounced	233 (12.0)	72	95	68 (5.2)	72	96	73 (6.7)	70	97
<b>Swelling</b>									
< 2.5 cm	196 (10.1)	52	68	139 (10.6)	48	86	138 (12.7)	48	86
2.5 - 5 cm	367 (3.0)	72	69	40 (3.0)	70	90	46 (4.2)	71	76
> 5 cm	233 (0.6)	71	83	9 (0.7)	112	78	19 (1.8)	109	90
<b>Redness</b>									
< 2.5 cm	204 (10.5)	46	97	152 (11.6)	47	96	117 (10.8)	47	96
2.5 - 5 cm	36 (1.9)	76	100	20 (1.5)	74	95	23 (2.1)	72	96
> 5 cm	10 (0.5)	70	90	12 (0.9)	130	92	8 (0.7)	78	100
<b>Swelling in the armpit</b>									
Mild	25 (1.3)	39	88	13 (1.0)	37	92	12 (1.1)	36	92
Moderate	10 (0.5)	50	80	6 (0.5)	55	100	5 (0.5)	48	80
Pronounced	4 (0.2)	102	100	0 (0.0)	NA	NA	2 (0.2)	95	100
<b>Total</b>	<b>1716 (88.5)</b>	<b>NA</b>	<b>NA</b>	<b>1046 (79.5)</b>	<b>NA</b>	<b>NA</b>	<b>859 (79.2)</b>	<b>NA</b>	<b>NA</b>

NA = not applicable.

The incidence of pain at the injection site and swelling increased with age (Appendix - Table 1). Similar to this age effect, late adopters in the catch-up campaign reported more pain at the injection site than participants of the regular NIP (Appendix - Table 2). Furthermore, late adopters reported slightly less local reactions than participants who started with vaccination in 2009 (Appendix - Table 2). For pain and reduced use of the arm the incidence after the second and third dose was lower than after the first dose, while the incidence of swelling was higher after the third dose than after the first (Appendix - Table 3).

#### 4.2.3 Systemic adverse events

Any systemic AEs was reported by 85.9% (95% CI 84.3-87.4) of the girls following the first dose, by 74.5% (95% CI 72.1-76.8) following the second dose, and following the third dose by 75.8% (95% CI 73.1-78.3). The most often reported systemic AEs were myalgia (64%), fatigue (24%) and headache (21%; Figure 4.2). These three events were reported by the same girl after all three doses in 39%, 7% and 4%, respectively.

The incidence proportion of systemic AEs is higher in girls with local reactions compared with girls without local reactions (86.4% vs. 60.3%,  $p < 0.001$ ). Higher proportions of systemic AEs were reported by girls with underlying illness (OR 1.3; 95% CI 1.1-1.7), headache, cold or flu during the week before vaccination (OR 2.5; 95% CI 1.8-3.6), and cold or flu at the time of vaccination (OR 4.2; 95% CI 3.1-4.8) compared with girls without the underlying illness, sickness before and at the time of vaccination, respectively.



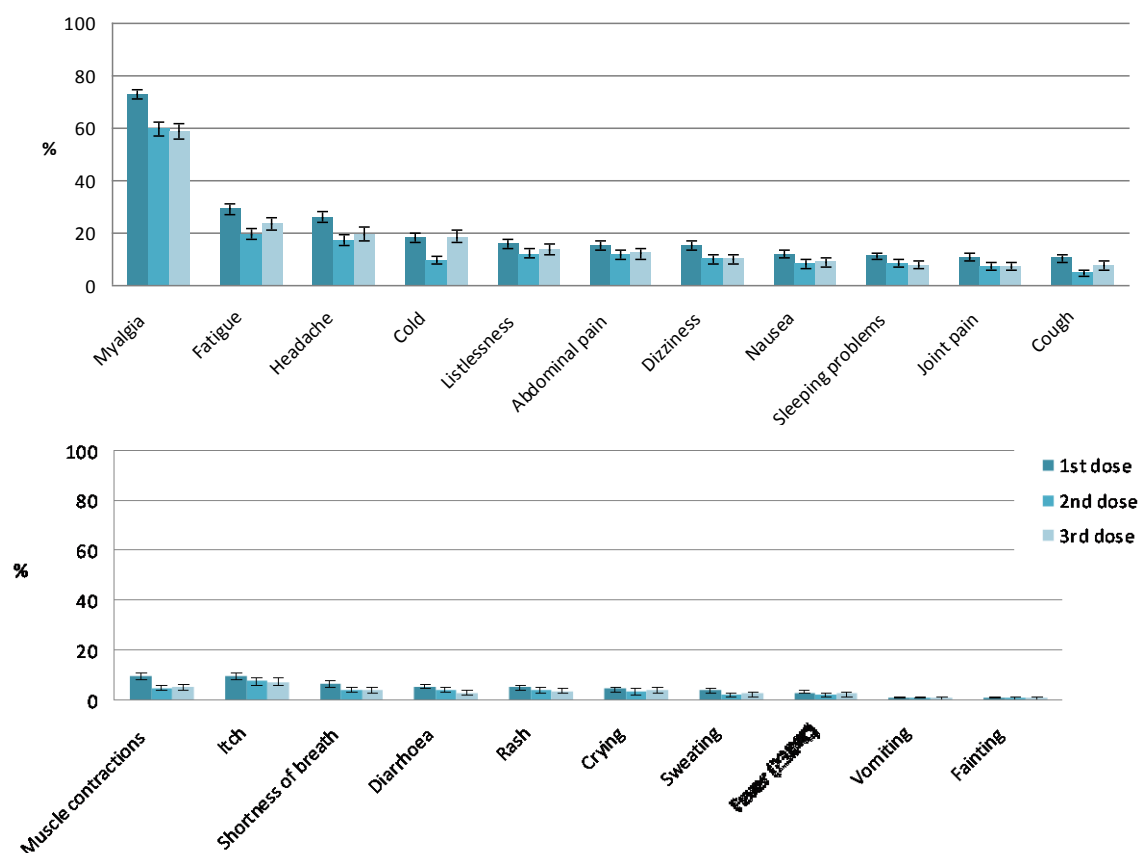


Figure 4.2 Incidence proportions of systemic AEs by dose, for cohorts 1993-1997

The proportions of the different systemic AEs starting within 24 hours, which therefore could possibly be related to the vaccination, ranged between 13% and 73% (Table 4.6). The median duration has a wide range, between immediate and 6 days depending on type of event, and was in most part similar for each dose or sometimes decreased with dose number (Table 4.6).

*Table 4.6 Number and proportion of reported systemic AEs with median duration and proportion starting within 24 hours after vaccination by dose, for cohorts 1993-1997*

Systemic AE	1 <sup>st</sup> dose			2 <sup>nd</sup> dose			3 <sup>rd</sup> dose		
	N (%)	Median duration	Start within 24 hrs (%)	N (%)	Median duration	Start within 24 hrs (%)	N (%)	Median duration	Start within 24 hrs (%)
Myalgia	1417 (73.0)	3 days	69	786 (59.8)	3 days	69	639 (58.9)	2 days	73
Fatigue	568 (29.3)	3 days	49	259 (19.7)	3 days	48	253 (23.3)	3 days	44
Headache	504 (26.0)	2 days	46	226 (17.2)	2 days	42	213 (19.6)	2 days	46
Cold	355 (18.3)	6 days	32	127 (9.7)	5 days	36	201 (18.5)	5 days	40
Listlessness	310 (16.0)	3 days	45	158 (12.0)	2 days	47	148 (13.7)	2 days	42
Abdominal pain	296 (15.3)	2 days	27	152 (11.6)	2 days	25	131 (12.1)	2 days	31
Dizziness	294 (15.2)	15-30 min	55	132 (10.0)	15-30 min	48	109 (10.1)	<15 min	50
Nausea	232 (12.0)	>30 min	49	107 (8.1)	15-30 min	49	97 (8.9)	>30 min	40
Sleeping problems	216 (11.1)	5 days	73	110 (8.4)	3 days	68	86 (7.9)	3 days	70
Joint pain	206 (10.6)	3 days	52	93 (7.1)	2 days	53	77 (7.1)	3 days	51
Cough	199 (10.3)	7 days	27	62 (4.7)	5.5 days	39	81 (7.5)	5 days	35
Muscle contractions	181 (9.3)	15-30 min	55	59 (4.5)	<15 min	59	53 (4.9)	<15 min	53
Itch	178 (9.2)	3 days	37	95 (7.2)	2 days	42	75 (6.9)	3 days	43
Shortness of breath	120 (6.2)	>30 min	51	51 (3.9)	15-30 min	43	40 (3.7)	<15 min	35
Diarrhoea	99 (5.1)	2 days	13	51 (3.9)	2 days	16	28 (2.6)	2 days	14
Rash	92 (4.7)	3 days	27	46 (3.5)	4 days	33	35 (3.2)	4 days	26
Crying	81 (4.2)	2 days	37	39 (3.0)	2 days	33	38 (3.5)	2 days	29
Sweating	68 (3.5)	15-30 min	38	23 (1.7)	15-30 min	35	25 (2.3)	15-30 min	48
Fever (≥ 38°C)	55 (2.8)	35.5 hrs	40	23 (1.7)	25.5 hrs	48	25 (2.3)	30 hrs	32
Vomiting	15 (0.8)	>30 min	33	11 (0.8)	<15 min	18	8 (0.7)	>30 min	38
Fainting	17 (0.9)	<15 min	29	8 (0.6)	<15 min	38	4 (0.4)	<15 min	50
Total	1667 (85.9)	NA	NA	980 (74.5)	NA	NA	822 (75.8)	NA	NA

NA = not applicable.

Some systemic AEs, including crying, cold, cough, shortness of breath, fatigue, sleeping problems, dizziness, and itch were dependent of age. In general, the incidence increased with age (Appendix - Table 4). Late adopters reported higher proportions of sleeping problems than girls of the regular NIP (OR 1.5). Also, girls who started already in 2009 reported more muscle contractions than girls of the regular NIP (OR 3.4) (Appendix - Table 5). For almost all systemic AEs the incidence proportions after the second and third dose were lower than after the first dose (Appendix - Table 6).

#### 4.2.4 Medical interventions

Analgesics, most often paracetamol, were used by 11.4% (95% CI 10.0-12.9) after the first dose, 8.3% (95% CI 6.9-9.9) after the second dose, and 11.3% (95% CI 9.6-13.4) after the third dose. The median duration was two days after the first dose and one day after the second and third dose.

In total 17 girls visited a GP, 6 (0.3%), 7 (0.5%), and 4 (0.4%) following the three subsequent doses, respectively. The most frequently reported reasons for visiting the GP were headache and rash. A medical specialist was visited once after the second dose and four times after the third dose, but in only one case a relation to the vaccination was considered possible. None of the girls visited the emergency room or was hospitalised.

#### 4.2.5 *Absence*

Girls reported to be absent from school, sports and/or other activities in 12.6%, 8.6%, and 13.1% following the three subsequent doses. The median duration of the absence was one day. In 1.4% a parent or guardian stayed at home from work to take care of the girl, also with a median duration of one day.

#### 4.2.6 *Background incidences of general symptoms*

At the time of the third vaccination round (autumn) an additional questionnaire was distributed among participants on general symptoms in the week before the vaccination. Some general symptoms, including fatigue, headache, cold, listlessness, abdominal pain, and cough, occurred more often before vaccination than after the vaccination (Figure 4.3).

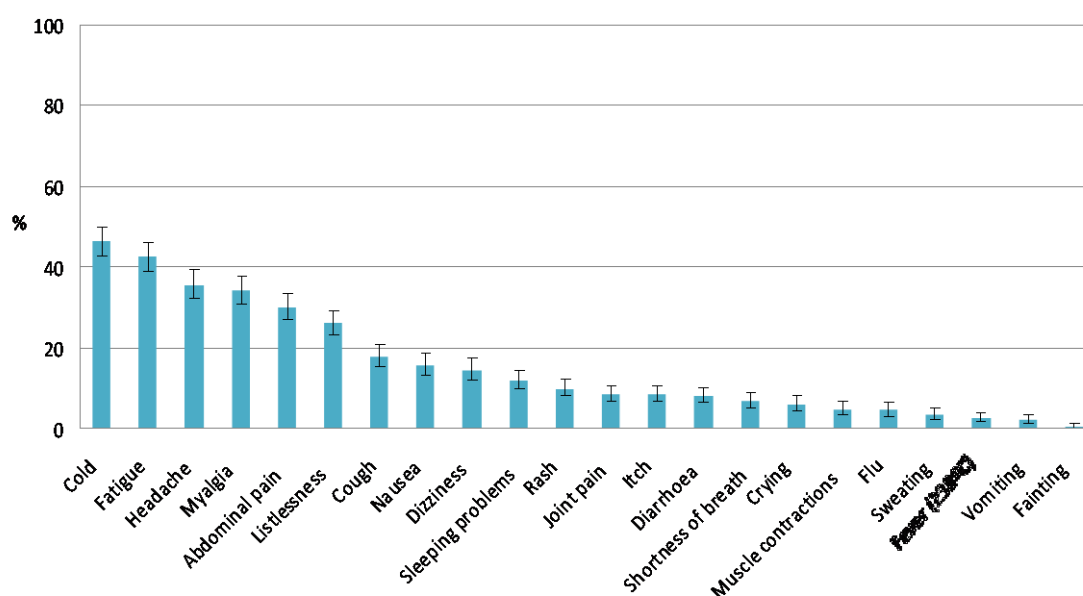


Figure 4.3 Incidence proportions of general symptoms before vaccination, for cohorts 1993-1997

An increasing trend with age was seen in the incidence proportions of listlessness, fatigue, sleeping problems, nausea, vomiting, dizziness, joint pain, muscle contractions, sweating, and itch before vaccination.

In the week before vaccination, 15.8% of the girls used analgesics and 4.1% visited the GP. Furthermore, 12.6% reported have been absent from school, sports and/or other activities in the week before vaccination and 2.4% of the parents stayed at home from work.

### 4.3 Discussion

During the HPV vaccination catch-up campaign in 2009 there was an increased adverse publicity focused on the safety of the vaccine. This was less in 2010, perhaps resulting in a somewhat lower response in this questionnaire study (65.0% versus 73.9% in 2009).

In the 2010 HPV vaccination campaign, lower proportions of AEs were reported compared with the 2009 campaign.<sup>3</sup> In 2010 girls reported slightly lower proportions of local reactions (88.5%, 79.5%, and 79.2% versus 92.1%, 79.4%, and 83.3% in 2009), especially the proportion which was classified as pronounced (17.2%, 12.6%, and 14.5% versus 28.7%, 16.6%, and 19.8% in 2009), and systemic AEs (85.9%, 74.5%, and 75.8% versus 91.7%, 78.7%, and 78.4% in 2009). Late adopters reported also slightly lower proportions of local reactions than girls who already started in 2009. This may be caused by an increased awareness of AEs in 2009 due to the media attention, and because it concerned a newly introduced vaccine.<sup>3</sup> In 2010, the vaccinated girls were younger (mainly 12-year-old) than the vaccinated girls in 2009 (13-16-year old), which also could have led to the reporting of less AEs.

The reporting of local reactions (82.4%) and systemic AEs (78.8%) was slightly higher than the reporting of these events after the Meningococcal serotype C (MenC) vaccination campaign in 2002 in the Netherlands. After one dose of the MenC vaccine, 12-to-16-year-old boys and girls reported local reactions in 58-77% and systemic AEs in 42-72%.<sup>21</sup>

Pain at the injection site was the most reported local reaction in our study (85.8%, 70.6%, and 70.2% after each dose respectively). This was similar to the proportions reported in several clinical trials on the safety and efficacy of the bivalent HPV vaccine (60.3% to 93.4%).<sup>16-18</sup> Also, studies in other countries showed comparable proportions of pain at the injection site (61.7% to 88.4%).<sup>19, 20</sup>

In our study myalgia was the most reported systemic AE (73.0%, 59.8%, and 58.9%). However, in the literature myalgia was less reported (13.9% - 52.2%).<sup>16-20</sup> An explanation for this difference is unclear, but it may be associated with the difference in the age groups studied; in the literature the girls aged 10 to 25 years, whereas we studied girls 12 to 16 years old. The occurrence of other frequently reported systemic events in our study, such as headache and fatigue, was comparable with that in the literature.<sup>16-20</sup>

Just like in the 2009 campaign, we found lower incidence proportions of some local reactions and almost all systemic AEs after the second and third dose compared with the first dose. A contributing factor could be that the immune response following the first contact differed from that after the consecutive doses. For inactivated vaccines like HPV, several doses are needed to stimulate the production of antibodies and memory cells. The type and concentration of mediators arising after each dose can differ from each other and thereby increase or decrease reactogenicity.<sup>22-26</sup>

In the reporting of AEs an age trend was observed. Older girls reported higher proportions of local reactions and systemic AEs than younger girls. In addition, this trend was also observed in the reporting of general symptoms in the week before vaccination. The same trend was also seen in the 2009 campaign and during the MenC vaccination campaign.<sup>3, 21</sup> This age effect may have been caused in part by more parents filling in the questionnaire for the younger girls

compared with the older girls, parents may report AEs different than the adolescents who report themselves. Unfortunately, we had no information on who completed the questionnaire.

Late adopters and girls that already started with vaccination in 2009 (birth cohorts 1993-1996) reported some AEs more often than girls of the regular NIP (birth cohort 1997). These differences were probably related to the increasing age trend in the reporting of AEs.

The frequency of symptoms could not be directly causally linked to the vaccination. Furthermore, the occurrence of general symptoms fluctuates over the year, depending on the season. Therefore we distributed an additional questionnaire on the occurrence of general symptoms in the week before the third vaccination. The results of this questionnaire demonstrate that some general symptoms occurred even more often before the third vaccination than after the third vaccination. Also, medical intervention was more frequently sought before vaccination than after vaccination. However, AEs following immunization may be unrelated to the vaccination, but can be experienced by the girls as associated to the vaccination, which may lead to vaccine refusal.

Selection bias may have been introduced because we investigated AEs with a questionnaire-based study. The frequency of AEs could have been overestimated when some girls, with no AEs experienced in the week after vaccination, did not return one or more questionnaire. However, analysis of the only girls who returned all three questionnaires gave no indication that girls who did not return all three questionnaires experienced either less or more AEs.

## 5 Conclusions

The continued safety surveillance of the HPV campaign in 2010 gives a good view on frequent and more rare solicited and unsolicited AEs after vaccination against HPV. In addition to the safety surveillance in 2009, not only girls aged 13 to 16 years (born in 1993-1996) were invited, but mainly 12-year-old girls (born in 1997). Furthermore, unlike in 2009, there was almost no adverse publicity in 2010. These conditions resulted in less reporting of AEs.

The reporting rate of immediate AEs was lower in 2010 compared with the catch-up campaign in 2009. In addition, the reporting rate of presyncope and syncope was also lower than in the 2009 HPV vaccination campaign. Also in 2010, the reporting rate of spontaneous reports following HPV vaccination was much lower compared with the 2009 HPV vaccination campaign. However, the percentage of causally related AEFI has increased compared with the 2009 HPV campaign. This probably indicates that professionals and public have more knowledge on true and perceived side effects of the HPV vaccine. However, it may also be a result of a declining reporting behaviour resulting in an increased underreporting. Furthermore, decreased media attention and rumour in 2010 compared to 2009 may play a role.

In the study on tolerability, local reactions, especially pronounced reactions, and systemic AEs were less often reported after HPV vaccination than in 2009, although AEs were still frequently reported by the girls. No serious or unexpected AEs were reported and almost all AEs were mild. These commonly occurring AEs were all transient.

We can conclude that in the catch-up campaign for girls aged 13 to 16 years (born in 1993 to 1996) and in the first year of the regular vaccination campaign for 12-year-old girls (born in 1997) with the bivalent HPV vaccine during mass vaccination no unexpected AEs after vaccination were found. Like with all vaccines it is important to keep the vigilance high for unexpected AEs after vaccination.

Results of this safety surveillance in the first period after introduction of HPV vaccination are used in communication to health care professionals and the public. The results will be presented on the website for professionals and in the information leaflet for girls and their parents. The aim is to contribute to confidence in the safety of HPV vaccination and vaccination in general.

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## List of abbreviations

AE	Adverse Event
AEFI	Adverse Events Following Immunisation
AR	Adverse Reaction
CI	Confidence Interval
CIb	Centre for Infectious Disease Control
GP	General Practitioner
HPV	Human papillomavirus
ITP	Idiopathic thrombocytopenic purpura
MenC	Meningococcal serotype C (vaccine)
MHS	Municipal Health Services
NIP	National Immunisation Programme
RIVM	National Institute for Public Health and the Environment, the Netherlands

## Appendix

*Table 1 Effect of birth cohort on the risk of local reactions (corrected for dose; ref = 1997)*

Local reaction	1996 <sup>a</sup>	1995 <sup>a</sup>	1994 <sup>a</sup>	1993 <sup>a</sup>
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Pain	1.05 (0.80-1.38)	1.57 (1.11-2.22)	1.94 (1.29-2.89)	1.65 (1.08-2.53)
Reduced use of the arm	0.93 (0.72-1.19)	0.86 (0.64-1.16)	1.01 (0.73-1.39)	1.52 (1.06-2.19)
Swelling	0.68 (0.47-0.99)	1.36 (0.94-1.96)	1.70 (1.15-2.49)	1.67 (1.09-2.54)
Redness	0.92 (0.65-1.30)	0.99 (0.67-1.47)	0.92 (0.60-1.44)	1.32 (0.85-2.05)
Swelling in the armpit	1.43 (0.69-2.94)	1.52 (0.67-3.46)	2.19 (1.01-4.77)	0.90 (0.27-3.02)
Total	1.05 (0.77-1.44)	1.29 (0.87-1.90)	1.85 (1.15-2.97)	1.73 (1.04-2.88)

<sup>a</sup>reference category: 1997.

*Table 2 Effect of vaccination schedule on the risk of local reactions (corrected for dose; ref = regular NIP participants)*

Local reaction	Started in 2009 <sup>a</sup>	Late adopter <sup>a</sup>
	OR (95% CI)	OR (95% CI)
Pain	1.75 (0.98-3.11)	1.35 (1.11-1.66)
Reduced use of the arm	1.70 (1.02-2.81)	0.93 (0.78-1.11)
Swelling	1.33 (0.73-2.42)	1.15 (0.92-1.45)
Redness	1.07 (0.54-2.09)	0.97 (0.77-1.23)
Swelling in the armpit	1.49 (0.33-6.76)	1.43 (0.86-2.39)
Total	3.51 (1.52-8.15)	1.21 (0.96-1.52)

<sup>a</sup>reference category: regular NIP (birth cohort 1997).

*Table 3 Effect of dose on the risk of local reactions (corrected for birth cohort; ref = 1<sup>st</sup> dose)*

Local reaction	2 <sup>nd</sup> dose <sup>a</sup>	3 <sup>rd</sup> dose <sup>a</sup>
	OR (95% CI)	OR (95% CI)
Pain	0.57 (0.48-0.67)	0.55 (0.46-0.67)
Reduced use of the arm	0.47 (0.40-0.55)	0.52 (0.44-0.61)
Swelling	1.06 (0.85-1.31)	1.50 (1.21-1.85)
Redness	1.10 (0.89-1.36)	1.06 (0.84-1.33)
Swelling in the armpit	0.70 (0.40-1.23)	0.86 (0.49-1.15)
Total	0.50 (0.41-0.61)	0.49 (0.39-0.60)

<sup>a</sup>reference category: 1<sup>st</sup> dose.

*Table 4 Effect of birth cohort on the risk of systemic AEs (corrected for dose; ref = 1997)*

<b>Systemic AE</b>	<b>1996<sup>a</sup></b>	<b>1995<sup>a</sup></b>	<b>1994<sup>a</sup></b>	<b>1993<sup>a</sup></b>
	<b>OR (95% CI)</b>	<b>OR (95% CI)</b>	<b>OR (95% CI)</b>	<b>OR (95% CI)</b>
Myalgia	1.19 (0.91-1.55)	1.32 (0.96-1.81)	0.80 (0.58-1.11)	1.34 (0.91-1.96)
Fatigue	0.98 (0.73-1.31)	1.40 (1.02-1.93)	1.41 (0.99-2.01)	1.60 (1.09-2.35)
Headache	0.95 (0.72-1.27)	1.16 (0.84-1.60)	1.39 (0.99-1.96)	1.55 (1.07-2.24)
Cold	0.81 (0.59-1.12)	1.31 (0.94-1.82)	1.31 (0.92-1.88)	1.50 (1.02-2.21)
Listlessness	0.92 (0.66-1.30)	1.29 (0.89-1.86)	1.44 (0.98-2.13)	1.41 (0.92-2.17)
Abdominal pain	0.93 (0.67-1.29)	0.86 (0.58-1.28)	0.91 (0.60-1.38)	1.10 (0.71-1.71)
Dizziness	0.82 (0.57-1.18)	1.34 (0.92-1.95)	1.65 (1.12-2.43)	1.29 (0.83-2.02)
Nausea	1.17 (0.82-1.68)	1.29 (0.86-1.94)	1.45 (0.95-2.23)	1.59 (1.01-2.51)
Sleeping problems	1.03 (0.70-1.52)	1.61 (1.09-2.40)	1.53 (0.99-2.38)	2.17 (1.39-3.39)
Joint pain	0.88 (0.58-1.32)	0.88 (0.55-1.41)	0.98 (0.59-1.61)	1.41 (0.87-2.29)
Cough	0.84 (0.55-1.27)	1.67 (1.12-2.48)	1.18 (0.74-1.90)	1.67 (1.05-2.68)
Muscle contractions	1.19 (0.79-1.81)	1.39 (0.87-2.22)	1.52 (0.93-2.50)	1.12 (0.62-2.00)
Itch	1.21 (0.81-1.81)	1.31 (0.83-2.06)	1.81 (1.15-2.83)	1.78 (1.09-2.92)
Shortness of breath	0.71 (0.40-1.26)	1.52 (0.91-2.53)	1.62 (0.94-2.79)	2.08 (1.20-3.62)
Diarrhoea	0.90 (0.53-1.54)	1.08 (0.60-1.95)	1.01 (0.52-1.94)	1.24 (0.64-2.41)
Rash	1.29 (0.77-2.17)	1.47 (0.82-2.63)	2.01 (1.14-3.54)	1.53 (0.77-3.04)
Crying	0.79 (0.43-1.44)	1.64 (0.96-2.82)	0.65 (0.28-1.52)	2.24 (1.25-4.00)
Sweating	0.86 (0.43-1.72)	1.55 (0.81-2.93)	1.30 (0.63-2.71)	1.28 (0.56-2.92)
Fever ( $\geq 38^{\circ}\text{C}$ )	0.76 (0.38-1.56)	1.30 (0.67-2.53)	0.70 (0.28-1.76)	1.54 (0.74-3.18)
Fainting	0.32 (0.04-2.36)	1.36 (0.40-4.60)	1.09 (0.25-4.67)	1.33 (0.31-5.71)
Total	1.23 (0.89-1.71)	1.37 (0.92-2.03)	1.14 (0.76-1.73)	2.11 (1.24-3.60)

<sup>a</sup>reference category: 1997.

*Table 5 Effect of vaccination schedule on the risk of systemic AEs (corrected for dose; ref = regular NIP participants)*

<b>Systemic AE</b>	<b>Started in 2009<sup>a</sup></b>	<b>Late adopter<sup>a</sup></b>
	<b>OR (95% CI)</b>	<b>OR (95% CI)</b>
Myalgia	1.81 (1.06-3.09)	1.07 (0.89-1.29)
Fatigue	1.18 (0.66-2.13)	1.22 (1.01-1.49)
Headache	1.17 (0.65-2.12)	1.18 (0.97-1.42)
Cold	1.18 (0.65-2.12)	1.12 (0.91-1.38)
Listlessness	1.01 (0.49-2.07)	1.20 (0.96-1.50)
Abdominal pain	0.90 (0.44-1.84)	0.91 (0.72-1.14)
Dizziness	1.11 (0.52-2.37)	1.19 (0.94-1.94)
Nausea	1.08 (0.49-2.39)	1.33 (1.05-1.70)
Sleeping problems	0.99 (0.40-2.42)	1.47 (1.15-1.88)
Joint pain	1.75 (0.83-3.70)	0.92 (0.70-1.20)
Cough	1.36 (0.62-3.00)	1.22 (0.94-1.59)
Muscle contractions	3.37 (1.60-7.10)	1.13 (0.84-1.52)
Itch	1.36 (0.58-3.19)	1.42 (1.09-1.86)
Shortness of breath	0.61 (0.14-2.62)	1.34 (0.97-1.85)
Diarrhoea	0.38 (0.05-2.84)	1.00 (0.70-1.42)
Rash	1.67 (0.56-4.99)	1.50 (1.05-2.13)
Crying	0.64 (0.15-2.75)	1.25 (0.87-1.79)
Sweating	2.31 (0.76-7.04)	1.08 (0.70-1.67)
Vomiting	1.50 (0.19-11.93)	0.92 (0.41-2.06)
Total	1.96 (0.99-3.91)	1.29 (1.02-1.62)

<sup>a</sup>reference category: regular NIP (birth cohort 1997).

*Table 6 Effect of dose on the risk of systemic AEs (corrected for birth cohort; ref = 1<sup>st</sup> dose)*

<b>Systemic AE</b>	<b>2<sup>nd</sup> dose<sup>a</sup></b>	<b>3<sup>rd</sup> dose<sup>a</sup></b>
	<b>OR (95% CI)</b>	<b>OR (95% CI)</b>
Myalgia	0.49 (0.42-0.58)	0.47 (0.39-0.56)
Fatigue	0.53 (0.44-0.64)	0.67 (0.55-0.81)
Headache	0.58 (0.48-0.70)	0.67 (0.55-0.81)
Cold	0.47 (0.37-0.58)	1.00 (0.82-1.22)
Listlessness	0.65 (0.52-0.81)	0.76 (0.61-0.95)
Abdominal pain	0.71 (0.57-0.88)	0.75 (0.59-0.94)
Dizziness	0.61 (0.48-0.76)	0.60 (0.47-0.77)
Nausea	0.64 (0.50-0.82)	0.72 (0.56-0.94)
Sleeping problems	0.72 (0.56-0.93)	0.65 (0.50-0.85)
Joint pain	0.61 (0.46-0.79)	0.60 (0.46-0.80)
Cough	0.43 (0.32-0.58)	0.70 (0.53-0.92)
Muscle contractions	0.44 (0.32-0.60)	0.47 (0.34-0.64)
Itch	0.75 (0.58-0.98)	0.71 (0.53-0.94)
Shortness of breath	0.60 (0.43-0.85)	0.57 (0.39-0.83)
Diarrhoea	0.75 (0.53-1.07)	0.49 (0.32-0.76)
Rash	0.73 (0.51-1.06)	0.64 (0.43-0.96)
Crying	0.70 (0.47-1.03)	0.83 (0.56-1.41)
Sweating	0.48 (0.29-0.77)	0.61 (0.38-0.98)
Fever ( $\geq 38^{\circ}\text{C}$ )	0.41 (0.25-0.67)	0.45 (0.28-0.72)
Vomiting	0.90 (0.39-2.06)	0.92 (0.38-2.24)
Fainting	0.70 (0.30-1.62)	0.43 (0.14-1.27)
Total	0.43 (0.35-0.53)	0.43 (0.34-0.53)

<sup>a</sup>reference category: 1<sup>st</sup> dose.



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