Vaccine 29 (2011) 4601–4607

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Reported adverse events in girls aged 13–16 years after vaccination with the human papillomavirus (HPV)-16/18 vaccine in the Netherlands

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ARTICLE INFO

Article history:
Received 17 December 2010
Received in revised form 7 April 2011
Accepted 17 April 2011
Available online 5 May 2011

Keywords:
Human papillomavirus
HPV vaccination
Tolerability
Adverse events following immunization

ABSTRACT

In 2009, human papillomavirus (HPV) vaccination was offered to girls born in 1993–1996 in a catch-up campaign, followed in 2010 by the implementation of the vaccination in the National Immunization Programme (NIP) for girls born in 1997. To monitor the tolerability of the 2009 catch-up campaign, we investigated the occurrence of adverse events within 7 days after vaccination with the bivalent HPV vaccine. A total of 6000 girls were asked to participate, including 1500 from each birth cohort from 1993 to 1996. One week after each of the required three successive doses, the participants received by e-mail a Web-based questionnaire focused on local reactions and systemic events. One or more questionnaires were returned by 4248 girls. Any local reaction was reported by 92.1% of the girls after the first dose, 79.4% after the second dose, and 83.3% after the third dose, and 91.7%, 78.7%, and 78.4% reported any systemic event after the three doses, respectively. Pain in the arm was the most frequently reported local reaction, of which 24.0%, 11.7%, and 14.7% was classified as pronounced. Myalgia was the most often reported systemic event. The proportion of local reactions and most systemic events was significantly lower after the second and third dose compared with the first dose (Odds ratio [OR], 0.33–0.76). Older girls reported a higher proportion of adverse events than younger girls. After vaccination with the bivalent HPV vaccine, girls 13–16 years of age reported a high proportion of short-term adverse events. These are maximum estimates and not necessarily caused by the vaccination itself. Although, girls experienced HPV vaccination as painful, no serious or unexpected adverse events were reported. The results of this survey are being communicated to health care workers and the public.

1. Introduction

In 2008, a decision was taken by the Ministry of Health, Welfare and Sport in the Netherlands to introduce vaccination against human papillomavirus (HPV) [1], because vaccination against HPV types 16 and 18 should protect against 70% of the cases of cervical cancer, thereby preventing hundreds of cervical cancer cases and about 100 deaths yearly. HPV vaccination was offered to girls born in 1993–1996 in 2009 in a catch-up campaign in advance of the regular campaign for girls born in 1997 begun in 2010. At present, Cervarix is used and given in three doses, at intervals of 0, 1, and 6 months [2].

Monitoring the vaccine's safety is an essential part of the post-marketing surveillance and the evaluation of the National Immunization Programme (NIP). The new target group and the limited data from clinical studies concerning girls aged 12–16 years stressed the importance of a study to address tolerability after implementation of mass vaccination in general practice in addition to the enhanced passive surveillance of adverse events. Such a tolerability study is an efficient and low cost tool for monitoring baseline rates of frequently occurring short-term adverse events as experienced by the girls. This method is very useful for monitoring variations in adverse events over time, for instance when the bivalent HPV vaccine might be replaced by the quadrivalent HPV vaccine, due to expiration of the current European tender.

Data from clinical trials regarding the safety and efficacy of the bivalent HPV vaccine showed that local reactions and systemic events frequently occurred after immunization [3–8]. These studies also demonstrated that older girls and women (15–25 years of age) reported a higher proportion of adverse events than younger girls (10–14 years of age) [3–7,9,10].

Improved knowledge of the occurrence of adverse events, including mild transient symptoms whether or not causal related to the vaccination, allows girls and parents to have correct information and expectations and thus helps prevent such potentialities as vaccine refusal. To assess the tolerability of the bivalent HPV vaccine after the catch-up campaign, we investigated the frequency

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doi:10.1016/j.vaccine.2011.04.050

and severity of adverse events as reported by 13-to-16-year-old girls within 7 days after each of the three successive HPV doses.

2. Methods

2.1. Vaccine

A bivalent HPV L1 virus-like particle vaccine targeted against HPV types 16 and 18 (Cervarix) was used in the campaign. Cervarix contains 20 μg HPV type 16-L1-protein, 20 μg HPV type 18-L1-protein, adjuvated with AS04, consisting of 50 μg 3-O-desacyl-4'-monophosphoryl lipid A (MPL) adsorbed on hydrated aluminium hydroxide (500 μg Al^{3+} in total). Three doses are recommended to be administered at intervals of 0, 1, and 6 months to induce optimal protection. In the catch-up campaign in 2009, the first dose was given in March or April, the second dose in April or May, and the third dose in September or October.

2.2. Participants

The catch-up campaign included girls from the birth cohorts 1993–1996. During the first vaccination session of this campaign, 1500 girls from each birth cohort at six vaccination sites in the central Netherlands were approached to participate in the study. E-mail addresses were collected from the girls who agreed to participate. Participants were asked to fill in a Web-based questionnaire 7 days after each of the three successive doses. If the questionnaire was not returned in 1.5 weeks, a reminder was sent by e-mail.

2.3. Questionnaire

The questionnaire asked about demographic characteristics (age, date, and location of vaccination), chronic illness (eczema, allergy, asthma, hay fever, and diabetes mellitus), and sickness during the week before vaccination (headache, cold, or flu) or at the time of vaccination (cold or flu). Girls were asked to report local reactions (swelling, redness, pain, swelling in the armpit, or reduced use of the arm) and systemic events (fever, listlessness, crying, cold, coughing, shortness of breath, fatigue, sleeping problems, nausea, vomiting, diarrhea, abdominal pain, headache, dizziness, fainting, myalgia, joint pain, muscle contractions, sweating, rash, or itch) that occurred within 7 days after vaccination. The severity of the local reactions such as swelling and redness was graded on a four-point scale: none, less than 2.5 cm (comparable to the size of a 2-euro coin), 2.5–5 cm, and more than 5 cm. For pain, swelling in the armpit, and reduced use of the arm the severity was graded as none, mild, moderate, or pronounced. Fever was reported as continuous, but it was presented as ≥38 °C, according to the criteria of the Brighton Collaboration [11]. Other systemic events were dichotomized (yes/no). Time interval and duration of symptoms were collected, as well as the use of analgesics, medical intervention, absence from school, sport or other activities, or a parent's or guardian's absence from work as the vaccinated girl's caretaker.

2.4. Statistical analysis

Proportions of local reactions and systemic events that occurred within 7 days after immunization were calculated with a 95% confidence interval (CI), median duration, and median onset time. To assess if the girls who did not return all three questionnaires were a specific subgroup we compared the results of all returned questionnaires after each dose with the results of the girls who returned all three questionnaires. Also, similarity in the reported adverse events between participants who complete the study and girls who dropped out of the study were determined. Furthermore, trends in the occurrence of adverse events between birth cohorts were analyzed with the chi-square test for trend. Using generalized linear mixed models (GLMM), we analyzed differences in the occurrence of adverse events after the three successive doses, corrected for birth cohort. Furthermore, the association between the occurrence of adverse events and the presence of chronic illness and sickness during the week before or at the time of vaccination, corrected for vaccination dose and birth cohort, was analyzed by GLMM.

3. Results

3.1. Response rate

In total, 5950 e-mail addresses were collected, of which 205 were incorrect. One or more questionnaires were returned by 4248 girls (73.9%), of whom 3946 (68.7%) returned the questionnaire after the first dose, 2725 (47.4%) after the second dose, and 2124 (37.0%) after the third dose (Table 1). All three questionnaires were returned by 1681 girls (29.3%).

3.2. Local reactions

After each of the three successive doses, one or more local reactions were reported in 92.1%, 79.4% and 83.3% of the girls, respectively (Table 2), from which 22.1%, 12.1%, and 14.8% were classified as pronounced. After the second and third dose, significantly lower proportions of local reactions were reported compared with the first dose (OR 0.33; 95% CI 0.28–0.38 and OR 0.43; 95% CI 0.37–0.51, respectively). Pain and reduced use of the arm were the most often reported local reactions. For all local reactions, a significant age trend was observed for the first and third dose, in that older girls reported a higher proportion compared with the younger girls (data not shown). From all local reactions, 99% started within 72 h after vaccination. The median duration of the local reaction increased when the local reaction was more pronounced (Table 2).

3.3. Systemic events

One or more systemic events were reported in 91.7%, 78.7%, and 78.4% of the girls, after each of the three successive doses (Table 3). Myalgia was the systemic event most often reported. Fatigue and headache were also frequently reported. For the systemic events, except for cold, cough, crying, fever and vomiting, the proportion was significantly lower after the second and third dose compared with the first dose (OR, 0.33–0.76) (Table 3). Fifty-one percent of the systemic events started within 24 h after immunization. Older girls reported having myalgia, fatigue, listlessness, dizziness, nausea, sleeping problems, cough, shortness of breath and diarrhea after the first dose significantly more often than younger girls (data not shown). After all three doses, girls who had local reactions reported systemic events more often (93.3%, 84.9%, and 83.4%, respectively) than girls who not had local reactions (72.2%, 54.6%, and 53.7%, respectively). This pattern was seen for almost all adverse events.

3.4. Sickness before or at the time of vaccination and the incidence of chronic illness

At the time of the first dose, 11.7% of the girls had a cold or flu, at the time of the second dose 13.0%, and at the third dose 19.5%. Girls with a cold or flu at the time of the vaccination reported a significantly higher proportion of local reactions except for swelling (OR, 1.24–1.70) and of systemic events except for vomiting, myalgia, muscle contractions, and itch (OR, 1.37–6.39) compared with girls without a cold or flu at the time of the vaccination (Table 4).

A headache, cold, or flu during the week before the vaccination was reported in 24.9%, 21.4%, and 29.0% of the girls for each of the

Table 1
Number of participants by birth cohort.

Birth cohort	1st dose (*n*)	2nd dose (*n*)	3rd dose (*n*)	Complete responders (*n*)
1993 (*n* = 1155)	1079	742	561	456
1994 (*n* = 1109)	1043	717	559	457
1995 (*n* = 1017)	940	637	508	387
1996 (*n* = 939)	859	621	490	377
Total (*n* = 4248; 73.9%)	3946 (68.7%)	2725 (47.4%)	2124 (37.0%)	1681 (29.3%)

three successive doses. Headache was the sickness reported most often before vaccination. Participants with a headache, cold, or flu during the week before vaccination reported a higher proportion of local reactions except for swelling in the armpit (OR, 1.27–1.68) and of systemic events except for fainting (OR, 1.27–4.49) compared with the girls without a headache, cold, or flu during the week before the vaccination (Table 4).

Chronic illness, including eczema, allergy, asthma, hay fever and diabetes mellitus, was present in 33.5% of all the participants. Eczema (14.4%) and allergy (12.8%) were the chronic illnesses most often reported. Girls with chronic illness reported a significantly higher proportion of the systemic events of fever, listlessness, cold, cough, shortness of breath, fatigue, sleeping problems, nausea, headache, dizziness, rash, or itch than girls without chronic illness (OR, 1.16–1.71) (Table 4).

3.5. Absence and interventions

Absence from school, sport, and/or other activities within 7 days after vaccination was reported in 15.9%, 7.2%, and 10.4% of the girls after the three doses, respectively. The median duration was two days. After each of the three doses, 2.1%, 0.9%, and 0.8% of the parents or guardians, were absent from work to take care of the vaccinated child.

Analgesics were used within 7 days after the first dose by 15.0% of the girls, after the second dose by 9.7%, and after the third dose by 11.0%. Paracetamol was the most used analgesic and the median duration was one day.

Within 7 days after each of the successive doses, 1.5%, 0.9%, and 1.1% of the girls needed medical intervention; most of them consulted the general practitioner (GP) by phone or visited the GP. Most girls required medical intervention because of the symptoms of fever, abdominal pain, headache, vomiting, dizziness, fainting, or rash. Some of the girls contacted their GP for information about the HPV vaccination and its possible adverse events. Two girls visited a specialist after the second dose. In one case causal association with the vaccination was possible. Four girls visited the emergency room within 7 days after vaccination. Follow-up information of the reported symptoms revealed that a causal relation with the vaccination was possible in only one case. In the other cases, either the interval was too long or there were other plausible explanations for the symptoms, or both. None of the girls was admitted to a hospital within the week after the vaccination.

4. Discussion

This study is one of the first population-based studies that assessed in detail the frequency of commonly occurring, short-term adverse events after mass vaccination in general practice with the bivalent HPV-16/18 vaccine. Our study showed that 13-to-16-year-old girls frequently experienced these adverse events after vaccination. Pain in the arm and myalgia were the adverse events most often reported. This is comparable with results from clinical trials of the bivalent HPV vaccine [5–8]. Our study showed a dose dependency of adverse events after vaccination. The proportion of reported adverse events was lower after the second and third dose than after the first dose. Also, we found a clear increasing trend in the incidence of adverse events by age. In general, the HPV vaccination was experienced as painful, but the adverse events were mostly mild and all transient.

Several clinical trials on the safety and efficacy of the bivalent HPV vaccine showed that pain was the most frequent local reaction occurring in 60.3–93.4% of cases [5–8]. This high frequency may be (partly) caused by the vaccination itself since the frequency of pain was also very high after receiving a placebo vaccine [5]. We found a comparable proportion of pain, however, the frequency of pronounced pain was higher in our study (between 11.7% and 24.0%) than in several trials (0.6%–16.3%) [5–8]. In these clinical trials, myalgia was the systemic event reported most often (16.7–52.2%) [5–8]. Girls in our study reported a higher proportion of myalgia after vaccination (>55%). An explanation for these differences is unclear, but it may be associated with the difference in the age groups studied; in the literature the girls aged 10–14 years and 15–25 years, whereas we studied girls 13–16 years old. Another possible explanation is the use of different case definitions for adverse events, which leads to different definitions of severity. This disparity is why the Brighton Collaboration has addressed the development of standardized case definitions for adverse events following immunization [12]. The occurrence of other frequently reported systemic events in our study, such as headache and fatigue, was comparable with that in the trials [5–8].

The high proportion of local reactions and systemic events that we found in this study is comparable to the proportion reported after the diphtheria, tetanus, and inactivated polio (dT-IPV) vaccination in the Netherlands. This vaccination is given to 9-year old children and is the last in the NIP before HPV vaccination [13]. Also, the proportions of pronounced pain were comparable (between 11.7% and 24.0% in our study vs. 20.2% after the dT-IPV vaccination). Furthermore, during the Meningococcal C vaccination campaign in the Netherlands in 2002, also high proportions of adverse events were reported in 13-16-year-olds (local reactions: 58–77%; systemic events: 45–72%).

Whereas the clinical trials on HPV vaccination has presented only the total proportion of adverse events after all three doses, we found a higher proportion of adverse events after the first dose compared with the second and third doses. Several explanations for this dose-dependent reaction are possible. Girls might have been more nervous just before receipt of the first dose, and the resulting tension might have caused more reaction, such as myalgia and pain. However, we have no scientific evidence for this. Another possible explanation is associated with the increased media attention when the vaccination campaign was first begun in 2009. Potentially, this could have led to an increased awareness of adverse events, which may have resulted in an overestimation of their occurrence. The influence of media attention will be evaluated in the future, since we performed the same study during the HPV vaccination campaign in 2010 (a year without increased media attention) among girls 13–16 years of age who opted not to participate in 2009 but chose to do so the next year. Another contributing factor could be that the immune response following the first contact varied from that after the second dose. For inactivated vaccines like HPV, in general, several doses are needed to stimulate the production of

Table 2
Occurrence of local reactions within 7 days after vaccination.

Local reaction and severity	1st dose (n = 3946)			2nd dose (n = 2725)				3rd dose (n = 2124)			
	% (95% CI)	Median onset time (in hours)	Median duration (in hours)	% (95% CI)	Median onset time (in hours)	Median duration (in hours)	OR[b] (95% CI)	% (95% CI)	Median onset time (in hours)	Median duration (in hours)	OR[b] (95% CI)
Pain							0.47 (0.41–0.53)				0.57 (0.49–0.65)
Mild	32.2 (30.7–33.6)	3.0	47.5	38.3 (36.5–40.2)	2.5	45.5		36.6 (34.5–38.7)	2.5	45.5	
Moderate	27.5 (26.1–28.9)	3.0	67.0	20.9 (19.4–22.5)	2.5	63.0		23.2 (21.4–25.0)	2.5	65.3	
Pronounced	24.0 (22.7–25.4)	2.5	84.0	11.7 (10.6–13.0)	2.0	81.0		14.7 (13.3–16.3)	2.0	83.0	
Reduced use of the arm							0.36 (0.33–0.40)				0.42 (0.37–0.47)
Mild	33.2 (31.8–34.7)	4.0	42.0	31.2 (29.4–32.9)	3.0	38.0		32.1 (30.1–34.1)	3.0	43.0	
Moderate	22.4 (21.1–23.7)	4.0	52.0	12.1 (10.9–32.9)	2.5	48.0		12.6 (11.2–14.1)	2.5	48.0	
Pronounced	15.7 (14.6–16.9)	3.0	71.8	5.5 (4.7–6.5)	2.8	73.0		7.5 (6.5–8.8)	2.0	72.0	
Swelling							0.93 (0.81–1.08)				1.35 (1.16–1.55)
<2.5 cm	11.5 (10.5–12.6)	5.0	48.0	10.6 (9.6–11.9)	4.0	48.0		14.3 (12.8–15.8)	4.0	48.0	
2.5–5 cm	3.5 (3.0–4.2)	5.0	71.5	3.8 (3.1–4.6)	5.0	57.0		4.8 (4.0–5.9)	5.0	67.5	
>5 cm	1.2 (0.9–1.6)	4.0	86.5	0.8 (0.5–1.2)	3.0	84.0		1.2 (0.8–1.8)	4.0	67.8	
Redness							1.06 (0.92–1.22)				0.95 (0.81–1.11)
<2.5 cm	12.2 (11.2–13.3)	5.0	46.0	13.6 (12.3–14.9)	3.0	48.0		12.2 (10.8–13.7)	4.0	47.6	
2.5–5 cm	2.2 (1.8–2.8)	6.5	76.5	1.7 (1.3–2.3)	4.0	60.0		1.6 (1.1–2.3)	5.5	72.0	
>5 cm	0.4 (0.3–0.7)	4.0	84.0	0.2 (0.1–0.5)	13.0	102.0		0.4 (0.2–0.8)	27.8	68.3	
Swelling in armpit							0.63 (0.42–0.95)				0.57 (0.49–0.65)
Mild	1.3 (1.0–1.8)	10.0	30.0	0.9 (0.6–1.4)	19.5	41.0		0.9 (0.6–1.5)	16.5	27.0	
Moderate	0.4 (0.2–0.6)	24.0	48.0	0.2 (0.1–0.5)	24.0	60.0		0.2 (0.1–0.5)	27.0	18.0	
Pronounced	0.2 (0.1–0.4)	24.0	63.0	0.1 (0.0–0.4)	108.0	74.0		0.0 (0.0–0.3)	42.0	96.0	
Total	92.1 (91.2–92.9)[a]			79.4 (77.8–80.9)			0.33 (0.28–0.38)	83.3 (81.7–84.9)[a]			0.43 (0.37–0.51)

[a] $p < 0.05$ for trend in the occurrence of local reactions between birth cohorts.
[b] Compared with the reference category: 1st dose.

Table 3
Occurrence of systemic events within 7 days after vaccination.

Systemic event	1st dose ($n = 3946$)			2nd dose ($n = 2725$)				3rd dose ($n = 2124$)			
	% (95% CI)	Median onset time (in hours)	Median duration	% (95% CI)	Median onset time (in hours)	Median duration	OR[b] (95% CI)	% (95% CI)	Median onset time (in hours)	Median duration	OR[b] (95% CI)
Myalgia	75.0 (73.6–76.3)[a]	4.0	3.0 days	55.4 (53.6–57.3)	4.0	3.0 days	0.38 (0.34–0.43)	56.5 (54.3–58.6)	4.0	3.0 days	0.39 (0.35–0.44)
Fatigue	33.9 (32.4–35.4)[a]	24.0	3.0 days	22.1 (20.5–23.7)	24.0	3.0 days	0.52 (0.46–0.59)	24.1 (22.3–26.0)	24.0	3.0 days	0.59 (0.52–0.67)
Headache	30.0 (28.6–31.5)	24.0	2.0 days	18.1 (16.6–19.6)	24.0	2.0 days	0.50 (0.44–0.56)	20.7 (19.0–22.5)	24.0	2.0 days	0.59 (0.52–0.67)
Cold	20.5 (19.3–21.8)	48.0	5.0 days	14.0 (12.7–15.4)	30.0	5.0 days	0.63 (0.55–0.72)	22.9 (21.1–24.7)	42.0	5.0 days	1.14 (0.99–1.30)
Dizziness	20.3 (19.1–21.6)[a]	11.0	15-30 min	9.9 (8.8–11.1)	24.0	<15 min	0.41 (0.36–0.48)	9.8 (8.6–11.2)	24.0	15-30 min	0.41 (0.35–0.49)
Listlessness	19.5 (18.3–20.8)[a]	24.0	2.0 days	13.5 (12.3–14.9)	24.0	2.0 days	0.60 (0.52–0.69)	11.8 (10.4–13.2)[a]	24.0	2.0 days	0.51 (0.44–0.61)
Abdominal pain	18.1 (16.9–19.3)	36.0	2.0 days	10.6 (9.5–11.9)	42.0	2.0 days	0.52 (0.45–0.61)	11.2 (9.9–12.6)[a]	30.0	2.0 days	0.55 (0.47–0.65)
Nausea	16.3 (15.2–17.5)[a]	24.0	<15 min	8.4 (7.4–9.6)	24.0	15-30 min	0.47 (0.40–0.55)	8.8 (7.7–10.1)	24.0	>30 min	0.49 (0.41–0.58)
Sleeping problems	14.2 (13.1–15.3)[a]	11.0	3.0 days	7.9 (6.9–9.0)	11.0	3.0 days	0.52 (0.43–0.61)	7.9 (6.8–9.2)	12.0	3.0 days	0.51 (0.43–0.62)
Joint pain	13.0 (12.0–14.1)	13.0	2.0 days	5.4 (4.6–6.3)[a]	24.0	2.0 days	0.38 (0.31–0.46)	4.8 (3.9–5.8)	8.0	3.0 days	0.33 (0.26–0.41)
Muscle contractions	12.0 (11.0–13.1)	8.0	<15 min	5.2 (4.4–6.1)	17.0	<15 min	0.38 (0.32–0.47)	4.5 (3.7–5.5)	24.0	<15 min	0.33 (0.26–0.41)
Cough	10.3 (9.4–11.3)[a]	48.0	5.0 days	7.7 (6.7–8.7)	30.0	5.0 days	0.72 (0.60–0.86)	11.7 (10.4–13.1)	42.0	5.0 days	1.14 (0.96–1.36)
Itch	10.1 (9.2–11.1)	24.0	2.0 days	7.0 (6.1–8.0)	24.0	2.0 days	0.66 (0.55–0.79)	6.6 (5.6–7.8)[a]	24.0	2.0 days	0.60 (0.49–0.74)
Shortness of breath	7.5 (6.7–8.4)[a]	30.0	<15 min	4.7 (3.9–5.5)	24.0	15-30 min	0.60 (0.48–0.74)	5.3 (4.4–6.3)	24.0	15-30 min	0.68 (0.54–0.86)
Rash	6.2 (5.4–7.0)	30.0	3.0 days	4.5 (3.8–5.4)	30.0	3.0 days	0.72 (0.57–0.90)	3.9 (3.1–4.8)	42.0	4.0 days	0.61 (0.47–0.79)
Diarrhea	5.1 (4.5–5.9)[a]	54.0	2.0 days	3.4 (2.8–4.2)	72.0	2.0 days	0.65 (0.51–0.84)	4.0 (3.2–4.9)	54.0	2.0 days	0.76 (0.59–0.99)
Sweating	4.9 (4.3–5.6)	30.0	15-30 min	2.6 (2.1–3.3)	30.0	15-30 min	0.51 (0.38–0.67)	2.7 (2.1–3.5)	30.0	15-30 min	0.52 (0.39–0.71)
Crying	4.4 (3.8–5.1)	36.0	3.0 days	3.7 (3.1–4.5)	48.0	3.0 days	0.85 (0.66–1.09)	3.8 (3.1–4.7)	45.0	3.0 days	0.87 (0.66–1.14)
Fever ($\geq$38 °C)	4.1 (3.5–4.7)	48.0	36.0 h	2.6 (2.1–3.3)[a]	36.0	37.0 h	0.64 (0.48–0.85)	4.0 (3.2–4.9)	30.0	36.0 h	0.97 (0.74–1.28)
Vomiting	1.6 (1.2–2.0)	78.0	<15 min	1.1 (0.7–1.5)	96.0	<15 min	0.67 (0.43–1.05)	1.2 (0.8–1.8)	51.0	<15 min	0.77 (0.49–1.23)
Fainting	1.1 (0.8–1.5)	10.0	<15 min	0.4 (0.2–0.7)	2.0	<15 min	0.35 (0.18–0.68)	0.6 (0.3–1.1)	30.0	<15 min	0.54 (0.29–0.99)
Total	91.7 (90.7–92.5)[a]			78.7 (77.1–80.2)			0.33 (0.28–0.38)	78.4 (76.6–80.2)			0.32 (0.27–0.38)

[a] $p < 0.05$ for trend in the occurrence of systemic events between birth cohorts.
[b] Compared with the reference category: 1st dose.

Table 4
Association between adverse events and chronic illness, sickness during the week before or at the time of vaccination.

Adverse event	Chronic illness		Sickness at the time of vaccination		Sickness during the week before vaccination	
	OR[a] (95% CI)	Significance	OR[b] (95% CI)	Significance	OR[c] (95% CI)	Significance
Swelling	1.15 (0.99–1.34)	0.059	1.17 (1.00–1.38)	0.052	1.27 (1.10–1.46)	<0.001
Redness	1.13 (0.98–1.31)	0.103	1.27 (1.08–1.49)	0.004	1.41 (1.22–1.62)	<0.001
Pain	1.09 (0.95–1.25)	0.222	1.39 (1.79–1.63)	<0.001	1.68 (1.46–1.94)	<0.001
Swelling in the armpit	1.36 (0.93–1.98)	0.113	1.70 (1.14–2.54)	0.010	1.50 (1.04–2.18)	0.032
Reduced use of the arm	1.09 (0.97–1.23)	0.162	1.24 (1.09–1.42)	0.002	1.45 (1.29–1.64)	<0.001
Fever (>38 °C)	1.48 (1.16–1.89)	0.002	2.69 (2.10–3.44)	<0.001	2.31 (1.82–2.92)	<0.001
Listlessness	1.16 (1.00–1.35)	0.049	1.88 (1.60–2.20)	<0.001	2.28 (1.99–2.62)	<0.001
Crying	1.09 (0.85–1.40)	0.483	1.66 (1.28–2.16)	<0.001	2.42 (1.93–3.04)	<0.001
Cold	1.27 (1.12–1.45)	<0.001	6.39 (5.59–7.29)	<0.001	4.49 (3.98–5.07)	<0.001
Cough	1.28 (1.09–1.51)	0.002	4.32 (3.69–5.06)	<0.001	3.49 (3.00–4.06)	<0.001
Shortness of breath	1.71 (1.40–2.10)	<0.001	2.44 (1.99–3.01)	<0.001	2.48 (2.05–3.01)	<0.001
Fatigue	1.23 (1.08–1.40)	0.002	1.95 (1.69–2.24)	<0.001	2.41 (2.13–2.72)	<0.001
Sleeping problems	1.30 (1.10–1.53)	0.002	1.68 (1.41–2.01)	<0.001	2.04 (1.74–2.38)	<0.001
Nausea	1.27 (1.09–1.48)	0.002	1.53 (1.29–1.80)	<0.001	2.22 (1.92–2.57)	<0.001
Vomiting	1.35 (0.91–1.99)	0.134	1.38 (0.89–2.16)	0.150	1.67 (1.14–2.46)	0.009
Diarrhea	1.10 (0.87–1.39)	0.404	1.43 (1.11–1.85)	0.006	1.71 (1.37–2.14)	<0.001
Abdominal pain	1.16 (0.99–1.34)	0.059	1.54 (1.31–1.80)	<0.001	2.14 (1.86–2.46)	<0.001
Headache	1.29 (1.14–1.46)	<0.001	1.70 (1.48–1.95)	<0.001	3.68 (3.26–4.14)	<0.001
Dizziness	1.29 (1.11–1.49)	<0.001	1.67 (1.43–1.96)	<0.001	2.37 (2.07–2.72)	<0.001
Fainting	1.14 (0.69–1.90)	0.607	2.34 (1.40–3.92)	0.001	1.45 (0.87–2.40)	0.155
Myalgia	1.07 (0.95–1.22)	0.275	1.15 (1.00–1.32)	0.054	1.27 (1.12–1.43)	<0.001
Joint pain	1.17 (0.98–1.40)	0.086	1.48 (1.21–1.80)	<0.001	1.53 (1.28–1.82)	<0.001
Muscle contractions	1.12 (0.93–1.34)	0.227	1.23 (1.00–1.51)	0.055	1.32 (1.10–1.58)	0.003
Sweating	1.20 (0.94–1.54)	0.150	1.37 (1.03–1.82)	0.031	1.62 (1.27–2.08)	<0.001
Rash	1.56 (1.27–1.93)	<0.001	1.64 (1.30–2.07)	<0.001	1.65 (1.34–2.03)	<0.001
Itch	1.43 (1.19–1.72)	<0.001	1.10 (0.89–1.36)	0.373	1.32 (1.10–1.58)	0.003

[a] Reference category: absence of chronic illness (eczema, allergy, asthma, hay fever, and diabetes mellitus).
[b] Reference category: absence of sickness at the time of vaccination (cold or flu).
[c] Reference category: absence of sickness during the week before vaccination (headache, cold or flu).

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 [14–18]. Whenever a first contact with a live attenuated vaccine results in an adequate immune response, reactogenicity after a booster dose usually is negligible.

An age trend was evident in the reported adverse events, in that older girls reported a higher proportion than the younger girls. The same trend was also seen for headache in the week before vaccination. When the proportion of adverse events reported in clinical trials for 10-to-14- year-old girls was compared with that of 15-to-25-year-old girls and women, the same effect was seen [5–7,9,10]. An age trend like this was also seen during the first campaign of Meningococcal C vaccination in the Netherlands in 2002. It is unknown whether this trend in adverse events can be explained as an effect of the vaccination. It may have been caused in part by more parents filling in the questionnaire for the younger girls compared with the older girls. Unfortunately, we had no information on who completed the questionnaire. Also, in regard to reported headaches, hormonal changes in adolescent girls apparently play a role in such sensitivity.

Because we investigated adverse events with a questionnaire-based study, selection bias may have been introduced. Girls that experienced adverse events in the week after vaccination were probably more likely to return the questionnaire than girls who did not experienced adverse events, but if and how much this possibly affect the results is not clear. The rates of adverse events we found in our study can be seen as maximum estimates. When we assume that all girls who did not return the questionnaire also did not experience adverse events, the minimum of local reactions are 63.3%, 37.6%, and 30.8% after the three doses, respectively. Minimum rates of systemic events are 63.0%, 37.3%, and 29.0% after the three successive doses. The response to the first questionnaire was rather high (68.7%) and even the minimum rates of adverse events are still substantial. However, the response rate decreased to 37.0% for the third questionnaire, resulting in a quite decrease in minimum rates, and only 29.3% returned all three questionnaires. Unfortunately, we were not able to contact the non-responders besides sending a reminder. However, after analysis we found that the proportion of reported adverse events with each dose was similar for all participants compared to the girls who returned all three questionnaires [19]. Girls who dropped out of the study showed the same pattern of adverse events as the girls who finished the study. So, we have no indication that girls who did not return all three questionnaires comprised a specific subgroup that experienced either fewer or more adverse events.

A limitation of the study is that we did not include an unvaccinated control group. Therefore, the frequency of symptoms could not be directly causally linked to the vaccination. However, adverse events 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. In addition, the questionnaire contained questions about the occurrence of some symptoms, such as headache, cold, or flu, before the vaccination. After vaccination, the occurrence of these symptoms increased from 21–29% to 27–39%. This demonstrates that the adverse events reported in our study were just partially caused by the vaccination itself. Girls reported a higher proportion of adverse events in the presence of chronic illness or sickness before or at the time of vaccination. Analysis of the proportion excluding these girls resulted in somewhat lower percentages of reported adverse events.

In conclusion, after vaccination with the bivalent HPV vaccine, girls aged 13–16 years reported particularly pain at the injection site and myalgia. We also found that adverse events after vaccination were dose dependent, in which the proportion decreased with dose. Furthermore, incidences of adverse events increased with the age of the girls. Adverse events were mostly mild, and all were transient. Although our findings are maximum estimates and many reported adverse events may be unrelated to the vaccination, these results are important to inform the target vaccination group and clinicians adequately which type of events may be expected after

vaccination. The results of this tolerability study will be presented on the Website (www.rivm.nl/hpv) for health care professionals, as well as in the information folder that is attached to the invitation letter for girls and their parents. Improved knowledge of adverse events could help increase confidence in HPV vaccination and in vaccination generally in the Netherlands. Besides that, the results are also useful for monitoring variations in rates of adverse events in the general population or in the target group over time.

Acknowledgement

We thank Sally Ebeling for the English editing.

References

[1] Dutch Health Council. Vaccination against cervical cancer. The Hague: Dutch Health Council; 2008. Publication No.: 2008/08. Dutch.
[2] de Melker HE, Conyn-van Spaendonck MAE, Boot HJ, Coutinho RA. Introduction of vaccination against cervical cancer. Ned Tijdschr Geneeskd 2009;153:A67 [Dutch].
[3] Paavonen J, Jenkins D, Bosch FX, Naud P, Salmerón J, Wheeler CM, et al. HPV PATRICIA study group. Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial. Lancet 2007;369(June (9580)):2161–70.
[4] Pedersen C, Petaja T, Strauss G, Rumke HC, Poder A, Richardus JH, et al. HPV Vaccine Adolescent Study Investigators Network. Immunization of early adolescent females with human papillomavirus type 16 and 18 L1 virus-like particle vaccine containing AS04 adjuvant. J Adolesc Health 2007;40(June (6)):564–71.
[5] Harper DM, Franco EL, Wheeler C, Ferris DG, Jenkins D, Schuind A, et al. GlaxoSmithKline HPV Vaccine Study Group. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. Lancet 2004;364(November (9447)):1757–65.
[6] Kim YJ, Kim KT, Kim JH, Cha SD, Kim JW, Bae DS, et al. Vaccination with a human papillomavirus (HPV)-16/18 AS04-adjuvanted cervical cancer vaccine in Korean girls aged 10–14 years. J Korean Med Sci 2010;25(August (8)):1197–204 [Epub 2010 July 21].
[7] Medina DM, Valencia A, de Velasquez A, Huang LM, Prymula R, García Sicilia J, et al. HPV-013 Study Group. Safety and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine: a randomized, controlled trial in adolescent girls. J Adolesc Health 2010;46(May (5)):414–21.
[8] Petäjä T, Keränen H, Karppa T, Kawa A, Lantela S, Siitari-Mattila M, et al. Immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine in healthy boys aged 10–18 years. J Adolesc Health 2009;44(January (1)):33–40.
[9] Reisinger KS, Block SL, Lazcano-Ponce E, Samakoses R, Esser MT, Erick J, et al. Safety and persistent immunogenicity of a quadrivalent human papillomavirus types 6, 11, 16, 18 L1 virus-like particle vaccine in preadolescents and adolescents: a randomized controlled trial. Pediatr Infect Dis J 2007;26(March (3)):201–9.
[10] Garland SM, Hernandez-Avila M, Wheeler CM, Perez G, Harper DM, Leodolter S, et al. Females united to unilaterally reduce endo/ectocervical disease (FUTURE) I Investigators. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med 2007;356(May (19)):1928–43.
[11] Marcy SM, Kohl KS, Dagan R, Nalin D, Blum M, Jones MC, et al. Brighton Collaboration Fever Working Group. Fever as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. Vaccine 2004;22(January (5–6)):551–6.
[12] Bonhoeffer J, Kohl K, Chen R, Duclos P, Heijbel H, Heininger U, et al. The Brighton Collaboration: addressing the need for standardized case definitions of adverse events following immunization (AEFI). Vaccine 2002;21(December (3–4)):298–302.
[13] Kemmeren JM, van der Maas NA, de Melker HE. Parental reports of adverse events following simultaneously given dT-IPV and MMR vaccines in healthy 9-year-old children. Eur J Pediatr Epub 2010 September 21.
[14] Vermeer-de Bondt PE, van der Maas NA. The effect of age and dose number on the risk of collapse (hypotonic-hyporesponsive episode) after pertussis vaccination. Pediatr Infect Dis J 2008;27(April (4)):355–7.
[15] Halperin SA, Scheifele D, Mills E, Guasparini R, Humphreys G, Barreto L, et al. Nature, evolution, and appraisal of adverse events and antibody response associated with the fifth consecutive dose of a five-component acellular pertussis-based combination vaccine. Vaccine 2003;21(June (19–20)):2298–306.
[16] Gold MS, Noonan S, Osbourn M, Precepa S, Kempe AE. Local reactions after the fourth dose of acellular pertussis vaccine in South Australia. Med J Aust 2003;179(August (4)):191–4.
[17] Jacquet JM, Bégué P, Grimprel E, Reinert P, Sandbu S, Silfverdal SA, et al. Safety and immunogenicity of a combined DTPa-IPV vaccine administered as a booster from 4 years of age: a review. Vaccine 2006;24(March (13)):2440–8.
[18] David S, Vermeer-de Bondt P, van der Maas N. Increase in localised symptoms in 4-year-olds following revaccination with DaPT-IPV. Ned Tijdschr Geneeskd 2010;154(A980) [Dutch].
[19] van't Klooster TM, Kemmeren JM, Vermeer-de Bondt PE, Oostvogels B, Phaff T, de Melker HE, et al. Human papillomavirus vaccination catch-up campaign in 2009 for girls born in 1993–1996 in the Netherlands: results of the post-marketing safety surveillance. Bilthoven; 2011. Report No.: 210012001.