Ministerie van Volksgezondheid,
Welzijn en Sport

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VOLKSGEZONDHEID
WELZIJN EN SPORT
27 JUNI 2016
SCANPLAZA

Directie Publieke Gezondheid
Crisisbeheersing en Infectieziekten

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981252-152001-PG

Correspondentie uitsluitend richten aan het retouradres met vermelding van de datum en het kenmerk van deze brief.

Datum 27 JUNI 2016
Betreft Adviesaanvraag HPV

Geachte heer Van Gool,

Op 31 maart 2008 heeft u in het rapport 'Vaccinatie tegen baarmoederhalskanker' geadviseerd vaccinatie tegen humaan papillomavirus (HPV), het virus dat baarmoederhalskanker veroorzaakt, in het Rijksvaccinatieprogramma te introduceren voor meisjes in de leeftijd van twaalf jaar.

HPV is de afkorting van humaan papillomavirus. Ongeveer 8 op de 10 vrouwen die seksueel actief zijn, krijgen ooit een HPV-infectie in hun leven. Meestal ruimt het lichaam dit virus binnen twee jaar weer zelf op. Soms blijft het virus aanwezig. Dan kan een voorstadium van baarmoederhalskanker en later kanker ontstaan. Het HPV-vaccin beschermt tegen twee gevaarlijke HPV-varianten (type 16 en 18). Deze veroorzaken samen 70% van alle gevallen van baarmoederhalskanker. Er is geen garantie op het voorkomen van baarmoederhalskanker met vaccinatie, maar vaccinatie leidt wel tot betere bescherming.

Naar aanleiding van het advies van de Gezondheidsraad, is in 2009 een eenmalige vaccinatiecampagne georganiseerd voor oudere meisjes (geboren in 1993-1996). Vanaf 2010 is HPV-vaccinatie opgenomen in het RVP voor meisjes van 12 jaar (in het jaar dat zij 13 jaar worden). De meisjes geboren tussen 1997-2000 kregen een 3 doses-vaccin aangeboden. Vanaf 2014 krijgen meisjes die geboren zijn na 2000 een 2 doses vaccin aangeboden, die even goede bescherming geven als het 3 doses vaccin, op voorwaarde dat meisjes de eerste vaccinatie krijgen voor hun 15e verjaardag.

In een recent advies pleit de Britse Throat Cancer Foundation ervoor om ook jongens te vaccineren tegen HPV. Tot nu toe gebeurt dat onder meer in Australië, de Verenigde Staten en Oostenrijk. Argumenten voor vaccinatie zijn vooral het voorkomen van aandoeningen die veroorzaakt worden door HPV, zoals genitale wratten en anale- en mond- en keelkankers. De vaccinatie van jongens zou ook de impact van de vaccinatie van meisjes versterken door een zogenaamde kudde-immuniteit (doordat veel mensen gevaccineerd zijn, komt het wilde virus minder voor).

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Sinds uw advies uit 2008 heeft geen advisering meer over HPV-vaccinatie plaatsgevonden door de Gezondheidsraad. Gezien het beschikbaar komen van nieuwe informatie in de EPAR- documentatie voor de al beschikbare vaccins en registratie van een nieuw nonavalent HPV-vaccin in 2016 vraag ik u nogmaals om uw oordeel over de vaccinatie tegen HPV. Hierbij verwijs ik u naar de notitie 'HPV-vaccination in the Netherlands' die het RIVM ook aan gezonden heeft (zie bijlage). Ik verzoek u de wenselijkheid van vaccinatie van jongens mee te nemen in uw oordeel.

Adviesaanvraag Gezondheidsraad en verzoek aan de Gezondheidsraad en het Zorginstituut tezamen.
Ik vraag de Gezondheidsraad om advies uit te brengen over HPV vaccinatie bij pubers en verzoek de Gezondheidsraad en het Zorginstituut een gezamenlijke notitie te leveren die een uitspraak doet over de gezondheidswinst die met een eventuele aanpassing van het vaccinatiebeleid te behalen is. Hierbij vraag ik om uw overwegingen expliciet te maken.

Ik verzoek u mij zo spoedig mogelijk van een advies te voorzien. Daarbij verzoek ik u om in een reactie aan te geven wat de planning voor dit adviestraject is en wanneer ik uw advies kan verwachten.

Een brief met dezelfde inhoud is ook gestuurd aan de heer A.H.J. Moerkamp van het Zorginstituut Nederland (zie bijlage).

Hoogachtend,

de minister van Volksgezondheid,
Welzijn en Sport,

mw. drs. E.I. Schippers

Ministerie van Volksgezondheid,
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Datum 27 JUNI 2016
Betreft Adviesaanvraag HPV

Geachte heer Moerkamp,

Op 31 maart 2008 is in het rapport 'Vaccinatie tegen baarmoederhalskanker' van de Gezondheidsraad geadviseerd vaccinatie tegen humaan papillomavirus (HPV), het virus dat baarmoederhalskanker veroorzaakt in het Rijksvaccinatieprogramma te introduceren voor meisjes in de leeftijd van twaalf jaar.

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In een recent advies pleit de Britse Throat Cancer Foundation ervoor om ook jongens te vaccineren tegen HPV. Tot nu toe gebeurt dat onder meer in Australië, de Verenigde Staten en Oostenrijk. Argumenten voor vaccinatie zijn vooral het voorkomen van aandoeningen die veroorzaakt worden door HPV, zoals genitale wratten en anale- en mond- en keelkankers. De vaccinatie van jongens zou ook de impact van de vaccinatie van meisjes versterken door een zogenaamde kudde-immuniteit (doordat veel mensen gevaccineerd zijn, komt het wilde virus minder voor).

Sinds het advies uit 2008 heeft geen advisering meer over HPV-vaccinatie plaatsgevonden door de Gezondheidsraad. Gezien het beschikbaar komen van

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nieuwe informatie in de EPAR- documentatie voor de al beschikbare vaccins en registratie van een nieuw nonavalent HPV-vaccin in 2016 heb ik de Gezondheidsraad nogmaals gevraagd om een oordeel over de vaccinatie tegen HPV. Ik heb daarbij ook verwezen naar de notitie 'HPV-vaccination in the Netherlands' die het RIVM ook aan de Gezondheidsraad heeft gezonden (zie bijlage). Ik heb de Gezondheidsraad verzocht ook de wenselijkheid van vaccinatie van jongens mee te nemen in haar oordeel.

Adviesaanvraag Gezondheidsraad en verzoek aan de Gezondheidsraad en het Zorginstituut tezamen.
Ik heb de Gezondheidsraad gevraagd om advies uit te brengen over HPV vaccinatie bij pubers en verzoek het Zorginstituut en de Gezondheidsraad een gezamenlijke notitie te leveren die een uitspraak doet over de gezondheidswinst die met een eventuele aanpassing van het vaccinatiebeleid te behalen is. Hierbij vraag ik om uw overwegingen expliciet te maken.

Ik verzoek u de planning van uw advies zo veel mogelijk af te stemmen op de advisering door de Gezondheidsraad over dit onderwerp.

Een brief met dezelfde inhoud is ook gestuurd aan de heer W.A. van Gool van de Gezondheidsraad (zie bijlage).

Hoogachtend,

de minister van Volksgezondheid,
Welzijn en Sport,

Mw. drs. E.I. Schippers

20 april 2016

HPV vaccination in the Netherlands:

Clinical efficacy, immunogenicity, safety and estimated impact of the HPV-vaccines licensed for use in pre-adolescent girl

Document prepared by:

Hans Bogaards, Robine Donken, Audrey King, Fiona van der Klis, Tessa Schurink, Venetia Qendri, Hester de Melker

INTRODUCTION

HPV vaccination in the Dutch National Immunisation Program

The current Dutch vaccination policy on HPV-vaccination is based on the advice of the Dutch Health Council out of 2008 entitled "Vaccination against cervical cancer" and the ministerial decision in January 2014 allowing a two-dose vaccination schedule. In 2009 a catch-up campaign was carried out offering vaccination to girls born in 1993-1996 (**1**; ref GR advise). From 2010 onwards girls were offered vaccination at 12 years of age (in the year they turn thirteen). The cohorts born in 1997-2000 were offered three doses (0, 1 and 6 months - bivalent vaccine). After the registration of the bivalent vaccine in a two-dose schedule in 2014, 12-year-old girls (i.e. born in 2001 and later) are offered a two-dose schedule (0, 6 months) of the bivalent HPV-vaccine (Figure 1).

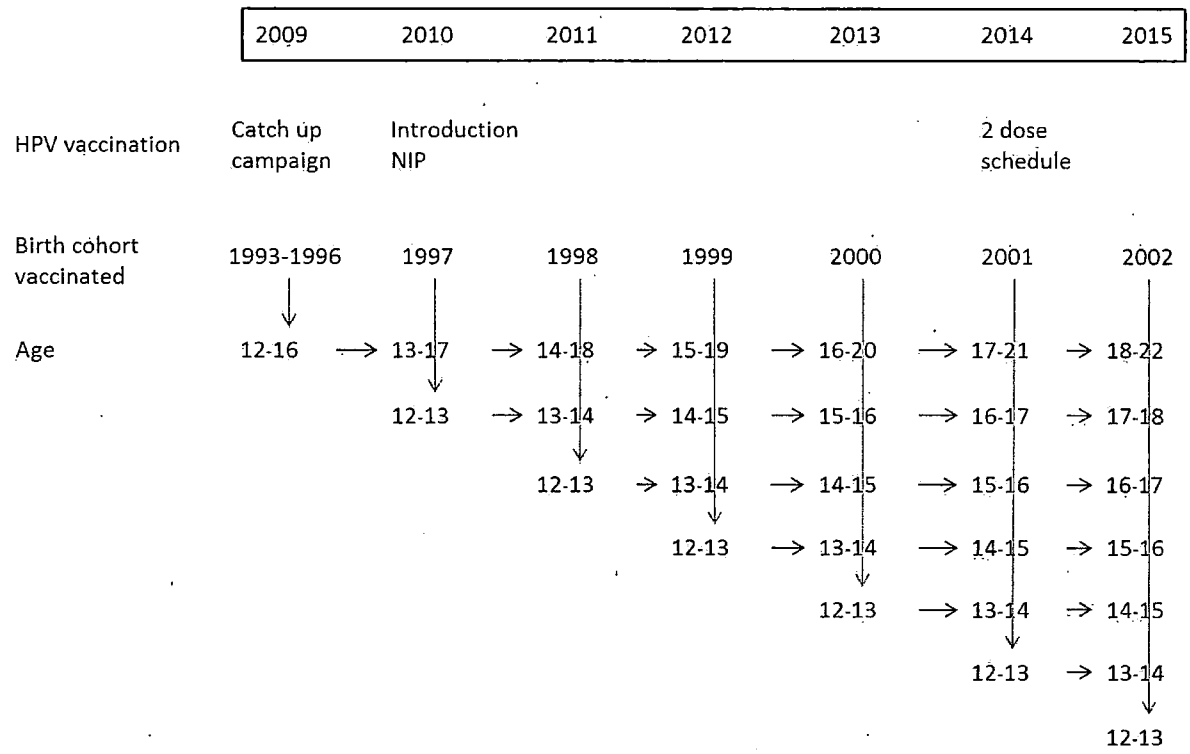

Figure 1. Overview HPV-vaccination according to birth cohort and vaccination schedule

Available vaccines

At this moment, three vaccines are licensed for the European market, which aim to prevent cervical cancer. These vaccines primarily differ in the number of HPV-types included in their composition and in cross-protective efficacy against related HPV-types (see Table 1). The licensed vaccines, their composition, immunization schedule and indications are shown in Table 2

Immunobridging for vaccine efficacy

For licensure, the data on clinical efficacy in individuals above the age of fifteen was used, as well as the data on immunogenicity in individuals above the age of fifteen and from nine to fourteen years of age. Licensure was based on the so-called immunobridging principle, which assumes non-inferior clinical efficacy of a vaccine in a specific age group when the antibody levels of the vaccine in that age group are non-inferior to the antibody levels in an age group where clinical efficacy has been shown.

Registration of the reduced dosing schedule was also based on non-inferiority results from immune-bridging studies, comparing antibody levels after a two-dose schedule in nine to fourteen year-olds to antibody levels after a three-dose schedule in fifteen to twenty-five year-olds **(2-6) (ref EMA assessment reports**

Table 1. Terminology

Term	Description
HPV2v	Bivalent HPV-vaccine (Cervarix®, GSK) providing direct protection against HPV-16/18 and significant cross-protection to HPV-6/11/31/33/39/45/51
HPV4v	Quadrivalent HPV-vaccine (Gardasil®, Merck) providing direct protection against HPV-6/11/16/18 and significant cross-protection to HPV-31
HPV9v	Nonavalent HPV-vaccine (Gardasil9®, Merck) providing direct protection against HPV-6/11/16/18/31/33/45/52/58
CIN2	cervical intraepithelial neoplasia stage II
CIN3	cervical intraepithelial neoplasia stage III
CxCa	invasive cervical carcinoma
Cervical disease	Diagnoses related to cervical carcinogenesis that require direct medical treatment according to screening guidelines, i.e. CIN2 or more advanced
VaCa	invasive vaginal carcinoma
VCa	invasive vulvar carcinoma
Aca	invasive anal carcinoma

Table 2. Available HPV-vaccines: composition, immunisation schedule and indications.

Vaccine name	HPV-types	Composition	Adjuvant	Number of doses	Registered indications								
					CIN	Cx Ca	VIN	VaIN	AIN	AC a	VC a	Va Ca	GW
Cervarix ®	HPV16/18	20 µg HPV16 L1 protein 20 µg HPV18 L1 protein	ASO4	9-14 yr. 2 Doses ≥15 yr. 3 Doses	x	x	x	x					
Gardasil ®	HPV6/11/16/18	20 µg HPV6 L1 protein 40 µg HPV11 L1 protein 40 µg HPV16 L1 protein 20 µg HPV18 L1 protein	AAHS	9-13 yr. 2 Doses ≥14 yr. 3 Doses	x	x	x	x	x	x			x
Gardasil 9®	HPV6/11/16/18/31/33/45/52/58	30 µg HPV6 L1 protein 40 µg HPV11 L1 protein 60 µg HPV16 L1 protein 40 µg HPV18 L1 protein 20 µg HPV31 L1 protein	AAHS	9-13 yr. 2 Doses ≥14 yr. 3 Doses	x	x	x	x	x	x	x	x	x

	20 µg HPV33 L1 protein 20 µg HPV45 L1 protein 20 µg HPV52 L1 protein 20 µg HPV58 L1 protein

CIN= Cervical intraepithelial neoplasia, CxCa= Cervix carcinoma, VIN= Vulvar intraepithelial neoplasia, VaIN= Vaginal intraepithelial neoplasia, AIN= Anal intraepitheliale neoplasia, ACa= Anus carcinoma, GW= genital warts, VCa= Vulvar carcinoma, VaCa= vaginal carcinoma

Aim of this report

The first part this report summarizes published data on clinical efficacy, immunogenicity and safety. Unless otherwise specified data was obtained from EMA EPAR documentation **(2-6)**

In the second part of this report, we present estimates of the directly preventable burden of cervical disease in the Netherlands according to the three available vaccines. The cervical cancer-incidence and mortality data used in this part of the report was obtained from the IKNL for the period 2005-2014 and 2003-2012 respectively. The CIN2+ data was based on the current cytology-based Dutch screening program for cervical cancer for the years 2008-2013. Although HPV-vaccination policy in the Netherlands is primarily aimed at the prevention of cervical disease, the available vaccines are also registered to prevent against (pre-cursors of) vaginal, vulvar or anal cancer. For this reason we also present the potential impact of the three available vaccines on vaginal, vulvar and anal cancer.[1] The data on vaginal, vulvar and anal cancer incidence and survival was again obtained from the IKNL for the period 2005-2014 and 2003-2012 respectively (cijfersoverkanker.nl).

The second part of the report consists of three sections:

1) Description of the annual incidence of cervical disease and of vaginal, vulvar and anal cancer per 100 thousand women in the Netherlands, stratified by relevant HPV-types
2) Estimation of the direct benefit per 100 thousand vaccinated girls in terms of protection against cervical disease, stratified by HPV-vaccine and by relevant HPV-types
3) Estimation of the direct benefit per 100 thousand vaccinated girls in terms of protection against cervical, vaginal, vulvar and anal cancer combined, stratified by HPV-vaccine

[1] [*Disclaimer: we will not report on the direct protection against genital warts, even though two of the three available vaccines are also registered for prevention of genital warts.*]

PART 1: DATA ON VACCINE EFFICACY, IMMUNOGENICITY AND SAFETY ACCORDING TO THE EMA

CLINICAL EFFICACY

The bivalent vaccine was evaluated among 15-25 year old women, which were included independent of baseline cytology, serology and HPV DNA status. For the quadrivalent and nonavalent vaccine efficacy was evaluated among 16-26 year olds who were included without pre-screening. Clinical efficacy as reported below is based on three dose schedule since non-inferiority of immunogenicity was shown for the two dose schedule (9-14 years) compared to the three dose schedule (15-25 years). The reported efficacies were based on the (adapted) per protocol analyses. The per protocol population for the bivalent vaccine included women who had received a completed three-dose regimen, were DNA negative and seronegative at month 0 and DNA negative at month 6. For the quadrivalent vaccine the per protocol population consisted of women who received three-doses within one year and were DNA negative from month 0 till month 7.

Vaccine types

Table 3 shows the HPV-type specific clinical efficacy of the three licensed HPV vaccines against CIN2+ as found in the according-to-protocol/per-protocol analysis (three dose schedule). The efficacy of the bivalent vaccine against vaccine types HPV16/18 was 94.9% (95% CI 87.7%-98.4%) and the efficacy of the quadrivalent vaccine against HPV16/18 was 98.2% (95% CI 93.5%-99.8%). For the nonavalent vaccine the efficacy against HPV16/18 was assumed to be equal to that of the quadrivalent vaccine based on immunobridging. For the five additional oncogenic types that are included in the nonavalent vaccine an efficacy of 97.1% (95%CI 83.5%-99.9%) was found after a three dose schedule.

Table 3. Vaccine efficacy of the licensed HPV-vaccines against CIN2+ (per-protocol (PP) analysis) as stated in the EMA EPAR documentation

HPV type	Clinical endpoint	Cervarix	Gardasil	Gardasil9
HPV16/18	CIN2+	94.9% (87.7%-98.4%)	98.2% (93.5%-99.8%)	* 98.2% (93.5%-99.8%)
HPV31/33/45/52/58	CIN2+			97.1% (83.5%-99.9%)
HPV31	CIN2+	87.5% (68.3%-96.1%)	55.6% (26.2%-74.1%)	
HPV33	CIN2+	68.3% (39.7%-84.4%)	19.1% (<0%-52.1%)	
HPV35	CIN2+	62.5% (<0%-93.6%)	13.0% (<0%-61.9%)	
HPV52	CIN2+	27.6% (<0%-59.1%)	14.7% (<0%-44.2%)	
HPV58	CIN2+	28.5% (<0%-65.7%)	31.5% (<0%-61.0%)	
HPV39	CIN2+	74.9% (22.3%-93.9%)	37.5% (<0%-69.5%)	
HPV45	CIN2+	81.9% (17.0%-98.1%)	0% (<0%-60.7%)	
HPV59	CIN2+	80.0% (<0%-99.6%)	39.9% (<0%-76.8%)	
HPV68	CIN2+	26.8% (<0%-69.6%)		
HPV51	CIN2+	54.4% (22.0%-74.2%)	16.3% (<0%-48.5%)	
HPV56	CIN2+	46.1% (<0%-81.8%)	-13.7% (<0%-32.5%)	
HPV66	CIN2+	56.4% (<0%-84.8%)		
HPV16/18	CIN3+	91.7% (66.6%-99.1%)	96.9% (88.4%-99.6%)	
HPV16/18	AIS		100% (30.6%-100%)	

* Efficacy assumed to be the same as after Gardasil

For both the bivalent and quadrivalent vaccine, also the efficacy against CIN3+ related to vaccine types HPV16/18 was reported after a three dose schedule. For the bivalent vaccine the vaccine efficacy after three doses was 91.7% (95% CI 66.6%-99.1%) and for the quadrivalent vaccine the efficacy was 96.9% (95%CI 88.4%-99.6%).

In addition to the efficacy against CIN2+ and CIN3+, an efficacy of 100% (95%CI 30.6%-100%) against adenocarcinoma is situ was reported for the quadrivalent vaccine.

Cross-protective efficacy against other types

For both the quadrivalent and the bivalent vaccine (both three dose schedule), some cross-protective efficacy has been shown against CIN2+ (table 3). For both vaccines there was a significant cross-protective efficacy against HPV31 related CIN2+, for the bivalent vaccine this was estimated at 87.5% (95% CI 68.3%-96.1%) and for the quadrivalent vaccine at 55.6% (95%CI 26.2%-74.1%). In addition to efficacy against HPV31 the bivalent vaccine shows significant cross-protection against HPV33 (68.3% 95% CI 39.7%-84.4%), HPV39 (74.9% 95%CI 22.3%-93.9%), HPV45 (81.9% 95%CI 17.0%-98.1%) and HPV51 (54.4% 95%CI 22.0%-74.2%).

Efficacy against any HPV type

For both the quadrivalent and the bivalent vaccine the vaccine efficacy against CIN2+ related to any HPV-type was shown using the three dose schedule. For the bivalent vaccine this was 64.9% (95% CI 52.7%-74.2%) in the per-protocol population. The quadrivalent vaccine showed an efficacy against any HPV-type of 42.7% (95%CI 23.7%-57.3%) in per-protocol (PP) analysis.

IMMUNOGENICITY

For all available HPV vaccines, no minimal antibody level associated with protection against precursor lesions or persistent infection has been identified so far.

Studies on the immune response to the bivalent vaccine (three doses) in 15-25 year olds have shown that 100% of participants remained seropositive for both vaccine types HPV16/18 (using the ELISA assay) at a median follow-up of 8.9 years. Additionally the geometric mean antibody titers (GMTs) for both vaccine types between months 107 and 113 after the first dose remained at least 10-fold higher than the GMTs observed in women who had cleared a natural infection. In a study evaluating the antibody responses after a two-dose schedule of the bivalent vaccine in 9-14 year old girls, all girls seroconverted for HPV16 and HPV18 one month after the second dose. Additionally non-inferiority of the two-dose schedule (9-14 year olds) to the response after three-doses (in 15-25 year olds) was shown at one month after the second dose.

For the quadrivalent vaccine, it was observed that for HPV16 99% and for HPV 18 60% of 16-23 year olds were respectively seropositive (using the cLIA; with IgG LIA 100% and 91%) up to nine years after vaccination (three doses) in the PP-population. In a study evaluating the antibody responses after a two-dose schedule in 9-13 year olds compared to the three-dose schedule in 16-26 year olds at month 7, the two-dose schedule was non-inferior to the three-dose schedule and remained non-inferior up to 36 months of follow-up.**(7)** (ref Dobson)

For the nonavalent vaccine persistence of antibody responses after 3 doses among 9-to 15-year olds was demonstrated for at least three years, with 93-99% of participants remaining seropositive, dependent on the HPV type. In 16-26 year olds, the response was shown up to 3.5 years with 78-98% of participants remaining seropositive, dependent on the HPV type.

SAFETY

In clinical studies of all three vaccines, the majority of adverse reactions was of mild to moderate severity and was not long lasting. Table 4 presents vaccine-related adverse reactions for the three vaccines. In studies of the bivalent vaccine, in which almost 80% of the girls were 10-25 years old, the most common adverse reaction was pain at the injection site (78%). In clinical trials of the quadrivalent and nonavalent vaccine, injection site reactions were also most common (77.1% and 84.8%, respectively).
In November 2015 the EMA concluded and reported that the evidence does not support that HPV vaccines cause chronic regional pain syndrome (CRPS) and Postural Orthostatic Tachycardia Syndrome (POTS). EMA stated that reports of CRPS and POTS were consistent with what would have been expected in this age group (**8**).

Table 4 Adverse reactions following HPV-vaccination from clinical trials and post-marketing surveillance

Adverse reaction	Cervarix	Gardasil	Gardasil9
Infections and infestations:			
Upper respiratory tract infection	Uncommon		
Injection-site cellulitis		*	*
Nervous system disorders:			
Headache	Very common	Very common	Very common
Dizziness	Uncommon	Common[1]	Common
Syncope sometimes accompanied by tonic-clonic movements	*	*	*
Acute disseminated encephalomyelitis		*	*
Guillain-Barré syndrome		*	*
Gastrointestinal disorders:			
Gastrointestinal symptoms including nausea, vomiting, diarrhoea and abdominal pain	Common	Common	Common
Skin and subcutaneous tissue disorders:			
Itching/puritus	Common	Common	
Rash	Common		
Utricaria	Common	Rare	
Musculoskeletal and connective tissue disorders:			
Myalgia	Very common	*	*
Arthralgia	Common	*	*
Pain in extremity		Common	
General disorders and administration site conditions:			
Injection site reactions including pain, redness, swelling	Very common	Very common	Very common
Fatigue	Very common	*	Common
Fever	Common	Common	Common
Injection site reactions such as induration, local paraesthesia	Uncommon		
At the injection site: pruritus, bruising			Common
Asthenia		*	*
Chills		*	*
Malaise		*	*
Blood and lymphatic system disorders:			
Lymphadenopathy	*	*	*
Idiopathic thrombocytopenic purpura		*	*
Immune system disorders:			
Hypersensitivity reactions including anaphylactic/anaphylactoid reactions	*	*	*
Angioedema	*		

Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000)

* Frequency cannot be estimated from the available clinical trial data

[1] Common in females, in males not observed more in vaccine recipients than in placebo recipients.

PART 2: DIRECT BENEFIT OF HPV VACCINATION AGAINST CERVICAL DISEASE AND OTHER ANOGENITAL CANCERS

Data used in this report was based on the current Dutch screening program for cervical cancer, which is cytology-based. Possible future reductions in CIN2+ or CxCa incidence resulting from HPV-based screening have not been taken into account. In addition, we assume that registration of the two-dose schedule for the nonavalent vaccine (Gardasil9®) will be accomplished within the time frame relevant for the tender procedure.

Section 1: Annual incidence of cervical disease and of vaginal, vulvar and anal cancer

The annual age-standardized incidence of cervical disease and of vaginal, vulvar and anal cancer per 100 thousand women in the Netherlands is given in Table 5. The ten-year survival probability for cancers diagnosed between 2004 and 2007 (relative to the expected survival in the Netherlands corrected for sex, age and calendar year) was 60% for CxCa, 35% for VaCa, 69% for VCa and 56% for ACa.

Table 5. Age-standardized incidence per 100 thousand women in the Netherlands

Diagnosis	Source	Calendar year						
		2008	2009	2010	2011	2012	2013	2014
CIN2	LEBA*	34	39	42	47	47	47	NA#
CIN3	LEBA	58	60	62	66	66	65	NA
CxCa	IKNL@	7.57	7.65	7.89	7.92	7.86	7.12	7.92
VaCa	IKNL	0.35	0.34	0.40	0.47	0.44	0.29	0.30
VCa	IKNL	2.39	2.97	2.87	3.16	2.80	2.69	3.22
Aca	IKNL	0.81	0.92	0.85	0.97	1.06	0.96	0.92

*LEBA: Landelijke Evaluatie van het Bevolkingsonderzoek Baarmoederhalskanker, 2014
#NA: not (yet) available
@IKNL: integraal kankercentrum Nederland, 2015

HPV is presumed to be the causative agent of all cervical disease. Genotype attribution in CIN2/3 was taken from a meta-analysis based on >14,000 histologically confirmed CIN2/3 cases (**9**) (Guan et al., Int J Cancer 2012). Genotype attribution of CxCa was taken from a retrospective worldwide study among >14,000 women with histologically confirmed cancer (**10**) (de Sanjosé et al., Lancet Oncol 2010) (Table 6).

The etiologic fraction due to HPV is 71% for VaCa (**11**) (Alemany et al., Eur J Cancer 2014), 18% for VCa (**12**)(de Sanjosé et al., Eur J Cancer 2013), and 88% for ACa (**13**) Alemany et al., Int J Cancer 2015). The type-distribution of HPV-positive cases is given in Table 5.

Table 6. HPV-type distribution of cervical disease and HPV-positive vaginal, vulvar and anal cancer

Diagnosis	HPV-type								
	HPV-16	HPV-18	HPV-31	HPV-33	HPV-39	HPV-45	HPV-51	HPV-52	HPV-58
CIN2*	39.8%	10.0%	11.6%	8.3%	5.4%	5.0%	9.7%	16.4%	12.1%
CIN3#	54.5%	4.9%	10.7%	11.0%	1.5%	1.7%	3.5%	10.9%	10.8%
CxCa	60.6%	10.2%	3.7%	3.8%	1.6%	5.9%	1.3%	2.8%	2.3%
VaCa@	57.4%	5.0%	5.3%	4.7%	2.0%	3.4%	2.4%	2.8%	1.0%
VCa@	72.5%	4.7%	1.0%	6.6%	0.7%	3.3%	--	1.9%	1.0%
ACa@	75.8%	3.4%	1.2%	2.3%	0.2%	0.9%	--	0.5%	1.9%

*HPV DNA tested from cells; 51% positive for multiple HPV-types

#HPV DNA tested from biopsies/tissue; 16% positive for multiple HPV-types

@HPV-positive cases only

Section 2: Direct benefit in terms of protection against cervical disease

We expanded a previously published Bayesian synthesis framework (**14**)(Bogaards et al., BMJ 2015) to calculate the direct benefit from preventing cervical disease by HPV-vaccination in a cohort of 100 thousand girls vaccinated at the age of twelve. We used publicly available (IKNL) cancer incidence and survival figures over the period 2005–2014 and 2003-2012 respectively, together with two-year cumulative outcomes of cervical screening rounds over the period 2008–2013 (LEBA) , and background mortality figures for the year 2010 (Statistics Netherlands). Without vaccination, we project an incidence of 700 lifetime cases of invasive cervical cancer in a cohort of 100 thousand twelve-year old girls, as well as 1,752 CIN2 and 2,830 CIN3 diagnoses if cytology-based cervical screening were to be continued.

The direct benefit from preventing cervical disease was calculated in two ways: (i) as the number of CIN2, CIN3 and CxCA diagnoses prevented by HPV-vaccination per 100 thousand vaccinated girls; and (ii) as the number of CxCA diagnoses prevented for each of the relevant HPV-types. Type-specific vaccine efficacies used in calculations are shown in Table 7 and were based on the data presented in part 1 (Table 3) and reported in the EPAR EMA on clinical efficacy. Only statistically significant type-specific vaccine efficacies were included. For the CIN2/3 cases, we corrected for the presence of multiple HPV-types by using a weighted efficacy for the proportion of CIN2/3 cases with multiple infections.

Table 7. Type-specific efficacy against HPV-positive CIN2+ (CIN2/3 or invasive carcinoma)

Vaccine	Efficacy								
	HPV-16	HPV-18	HPV-31	HPV-33	HPV-39	HPV-45	HPV-51	HPV-52	HPV-58
HPV2v	95%	95%	88%	68%	75%	82%	54%	--	--
HPV4v	98%	98%	56%	--	--	--	--	--	--
HPV9v	98%	98%	98%	98%	--	98%	--	98%	98%

The direct benefit of each HPV-vaccine regarding cervical disease prevention is given in Tables 8a, 8b. HPV9v is expected to provide the highest benefit to vaccinated girls, leading to a reduction of 75% of

CIN2 diagnoses, 88% of CIN3 diagnoses and 87% of CxCa cases. For comparison, HPV2v is expected to reduce CIN2 diagnoses by 56%, CIN3 diagnoses by 66%, and CxCa cases by 80% and HPV4V is expected to reduce CIN2 diagnoses by 41%, CIN3 by 55% and CxCa by 71%.

Table 8a. Number of CIN2, CIN3 and CxCa cases prevented per 100 thousand vaccinated girls

Vaccine	Diagnosed cases prevented (percentage of total)		
	CIN2*	CIN3*	CxCa
HPV2v	978 (56%)	1,879 (66%)	558 (80%)
HPV4v	715 (41%)	1,563 (55%)	499 (71%)
HPV9v	1,314 (75%)	2,504 (88%)	611 (87%)

*Diagnosed cases expected under cytology-based cervical screening

Table 8b. HPV-type distribution of cervical cancer cases prevented per 100 thousand vaccinated girls

Vaccine	CxCa cases prevented by HPV-type								
	HPV-16	HPV-18	HPV-31	HPV-33	HPV-39	HPV-45	HPV-51	HPV-52	HPV-58
HPV2v	402	68	23	18	8	34	5	0	0
HPV4v	415	70	14	0	0	0	0	0	0
HPV9v	415	70	26	26	0	40	0	19	15

Section 3: Direct benefit against cervical, vaginal, vulvar and anal cancer combined

We estimated the combined impact on cervical disease and other anogenital cancers under the assumption that the reported efficacies against cervical disease would also apply to other anogenital HPV-related disease. It should be noted from the outset that registered indications differ for the three HPV vaccines (Table 2) and that type-specific efficacies have not been estimated for all disease outcomes considered in this section. Table 9 gives the direct benefit of each HPV-vaccine regarding prevention of vaginal, vulvar and anal cancer using the type-specific vaccine efficacies shown in Table 7. In a cohort of 100 thousand twelve-year old girls, we project lifetime incidences of 59, 430 and 107 cases of vaginal, vulvar and anal cancer, respectively, in the absence of HPV-vaccination. Of these, 41 vaginal, 80 vulvar and 86 anal cases are attributable to HPV. The relative reductions in cancer incidence for each HPV-vaccine are given as a percentage of the total, irrespective HPV-attribution.

Table 9. Number of VaCa, VCa and ACa cases prevented per 100 thousand vaccinated girls

Vaccine	Non-cervical cancer cases prevented (percentage of total)		
	VaCa	VCa	Aca
HPV2v	28 (47%)	61 (14%)	71 (66%)
HPV4v	25 (42%)	56 (13%)	71 (66%)
HPV9v	30 (51%)	66 (15%)	76 (71%)

The direct benefit in terms of protection against cervical, vaginal, vulvar and anal cancer combined was estimated by calculating the number of life-years gained in a cohort of 100 thousand vaccinated girls. In this calculation, we used life expectancy figures for the year 2010 (Statistics Netherlands) in combination with the age distribution at cancer diagnosis and cancer-specific survival rates over the period 2005–2014 (IKNL). Table 10 shows the results.

Table 10. Number of life-years gained per 100 thousand vaccinated girls

Vaccine	Life-years gained from preventing cancer				
	CxCa	VaCa	VCa	ACa	TOTAL
HPV2v	4,640	280	310	590	5,810
HPV4v	4,160	240	272	605	5,277
HPV9v	5,100	293	313	650	6,356

Prevention of non-cervical anogenital cancers is expected to substantially increase the direct benefit from HPV-vaccination, amounting to a total of around 6,000 life-years per 100 thousand vaccinated girls. Of the three available HPV-vaccines, HPV9v is expected to provide the highest gain in life-years, achieving an almost 10% increase relative to HPV2v.

Conclusion

We based our estimates of direct vaccine impact on the currently available information published by the EMA in EPAR documentation used for vaccine registration, and on the type distribution for HPV-related anogenital diseases obtained from large-scale meta-analyses.

The estimated expected health gain is about 10% larger for the nonavalent vaccine compared to the bivalent vaccine, while the bivalent vaccine was estimated to have about 10% more health gain compared to the quadrivalent vaccine. The latter is due to higher cross-protection as reported in the EPAR documents.

HPV16 type is the most important type with regard to the disease burden for all HPV-related cancers. HPV18 is the second most important type for cervical cancer. In accordance with the Health Council Report prevention of genital warts was not included.

In our estimation no difference was assumed in the duration of protection for the three vaccines. There are no indications in the EPAR documents that protective efficacy decreases for the bivalent and quadrivalent HPV vaccine. After a follow-up of 9 years with Cervarix, 100% remained seropositive for both HPV16 and HPV18 as measured with ELISA. For Gardasil after a follow-up of 8 years, 97% and 64% remained seropositive for HPV 16 and 18, respectively as measured with cLIA. Data on the duration of protection for the nonavalent HPV vaccine is not yet available.

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