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

PROJECTED DIRECT BENEFIT OF VACCINATION AGAINST HPV-RELATED CANCER IN THE NETHERLANDS

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Introduction:

HPV vaccination policy in the Netherlands will be restructured from 2021 onward, following the decision of the State Secretary on Public Health, Welfare and Sports in September 2019 and based on the advice from the Dutch Health Council entitled "Vaccination against HPV" as of June 2019. From 2021 onward, girls and boys in the Netherlands will be invited to receive two doses of HPV vaccine six months apart in the year they turn ten years old. The Health Council did not advise on the choice of vaccine.

At this moment, three HPV vaccines are licensed for the European market. These vaccines primarily differ in the number of HPV types included in their composition and in cross-protective effectiveness against HPV types not included in the respective vaccines {see Terminology}.

Terminology

Term	Description
HPV2v	Bivalent HPV vaccine (Cervarix®, GSK) providing direct protection against HPV-16/18 and significant cross-protection to HPV-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, ie. CIN2 or more advanced
VaCa	Invasive vaginal carcinoma
VuCa	Invasive vulvar carcinoma
AnCa	Invasive anal carcinoma
PeCa	Invasive penile carcinoma
OroCa	Invasive oropharyngeal carcinoma

The focus of this document is to report on the direct protection (ie. the protection for the vaccinated individual, irrespective herd effects) against HPV-related cancer in the Netherlands. We consider all cancers with strong evidence for causal involvement of HPV in carcinogenesis. According to the International Agency for Research on Cancer (IARC) these are: cervical, vulvar, vaginal, anal, and oropharyngeal cancers in women; and penile, anal, and oropharyngeal cancers in men. None of the HPV vaccines is registered for prevention of oropharyngeal cancer, but this is mainly due to the lack of well-defined precursor lesions in the oropharynx. The evidence for causal involvement of HPV is not questioned, we will therefore also report on the direct protection against oropharyngeal cancer.[1]

This document contains three sections:

1) Description of the annual incidence of cervical disease and of vaginal, vulvar, anal, penile and oropharyngeal cancers per 100 thousand women or men in the Netherlands, stratified by relevant HPV types.
2) Estimation of the direct benefit in terms of protection against cervical disease and other HPV-related cancers per 100 thousand vaccinated girls, stratified by HPV vaccine and by relevant HPV types.
3) Estimation of the direct benefit in terms of protection against HPV-related cancers per 100 thousand vaccinated boys, stratified by HPV vaccine and by relevant HPV types.

To arrive at an overall benefit of vaccination, we sum the expected gain in life-years per vaccinated cohort, consisting of 100 thousand girls plus 100 thousand boys vaccinated at the age of nine years, for each of the available HPV vaccines. This summary measure accounts for differences in etiologic fractions and genotype attributions due to HPV, as well as differences in incidence, age distribution and mortality of the various HPV-related cancers.

Section 1: Annual incidence of cervical disease and of other HPV-related cancers

The age-standardized incidence of cervical disease and of vaginal, vulvar, anal and oropharyngeal cancers per 100 thousand women in the Netherlands is given in Table 1A. The age-standardized incidence of penile, anal and oropharyngeal cancers per 100 thousand men in the Netherlands is given in Table 1B.

[1] [*Disclaimer: we will not report on the direct protection against anogenital warts, even though HPV4v and HPV9v are registered for prevention of anogenital warts.*]

Table 1A. Age-standardized incidence per 100 thousand women in the Netherlands

Diagnosis	Source	Calendar year						
		2011	*2012*	*2013*	*2014*	*2015*	*2016*	*2017*
CIN2	LEBA[*]	45	45	45	45	47	49	NA[#]
CIN3	LEBA	64	64	63	64	66	68	NA
CxCa	IKNL[@]	7.83	7.88	7.15	8.06	7.67	8.83	8.33
VaCa	IKNL	0.48	0.44	0.30	0.32	0.42	0.34	0.42
VuCa	IKNL	3.16	2.83	2.72	3.24	2.85	3.00	2.87
AnCa	IKNL	0.96	1.16	0.95	0.96	1.16	1.20	1.04
OroCa	IKNL	1.98	2.04	1.88	1.90	1.66	1.82	1.68

[*]LEBA: Landelijke Evaluatie van het Bevolkingsonderzoek Baarmoederhalskanker, t/m 2017
[#]NA: not yet available; presumably higher than before due to introduction of HPV screening
[@]IKNL: Integraal Kankercentrum Nederland, 2019

Table 1B. Age-standardized incidence per 100 thousand men in the Netherlands

Diagnosis	Source	Calendar year						
		2011	*2012*	*2013*	*2014*	*2015*	*2016*	*2017*
PeCa	IKNL[@]	1.43	1.31	1.29	1.09	1.32	1.39	1.34
AnCa	IKNL	0.80	0.98	1.07	0.90	1.09	1.09	1.06
OroCa	IKNL	4.13	3.92	3.86	3.96	3.91	4.39	4.11

[@]IKNL: Integraal Kankercentrum Nederland, 2019

The 8-year survival probability for cancers diagnosed since 2008 (relative to the expected survival in the Netherlands corrected for sex, age and calendar year) was 63% for CxCa, 40% for VaCa, 65% for VuCa, 56% for AnCa, 70% for PeCa, and 38% for OroCa. Of note, HPV-induced oropharyngeal cancers have better prognosis than HPV-negative oropharyngeal cancers.

HPV is presumed to be the causative agent of all cervical disease. Genotype attribution in CIN2 and CIN3 was determined by a statistical method for estimating genotype attribution in high-grade lesions from cervical screening samples [1]. This method has been validated on 512 HPV-positive women referred for colposcopy and tested by laser-capture microscopy-PCR, considered the reference method for identifying the HPV genotype that is causally linked to CIN2+. Genotype attribution of CxCa was taken from a retrospective worldwide study among women with histologically confirmed cancer [2]. Given some discrepancies in the ranking of HPV types detected in CxCa across geographic regions, we conditioned our estimates on the 2058 cases of HPV-positive cervical cancer from Europe. Taken together, the HPV types relevant for

vaccination comprise 89% of diagnosed CIN2 cases, 91% of CIN3 cases, and 92% of CxCa cases {see Table 2A}.

Table 2A. HPV-type attribution in cervical disease

Diagnosis*	HPV type@								
	HPV α-7 species			HPV α-9 species					other
	HPV-18	HPV-39	HPV-45	HPV-16	HPV-31	HPV-33	HPV-52	HPV-58	HPV-51
CIN2*	5.7%	1.0%	1.8%	47.0%	15.0%	6.8%	4.2%	3.8%	3.5%
CIN3*	4.9%	<0.1%	1.3%	62.0%	7.2%	5.1%	3.1%	4.5%	2.8%
CxCa	7.3%	1.3%	3.9%	65.5%	3.4%	5.7%	1.9%	1.3%	1.4%

*Cases detected via cervical screening
@Oncogenic HPV types relevant for HPV vaccination only

The etiologic fraction due to HPV has been estimated at 71% for VaCa [3], 18% for VuCa [4], 88% for AnCa [5], and 32% for PeCa [6]. The latter figure is conditioned on penile cancer cases from Europe, to account for substantial geographic variation. Likewise, the etiologic fraction for oropharyngeal cancer varies widely, and has been estimated at 34% among men and 23% among women in the Netherlands since 2000 [7]. The type-distribution of the corresponding HPV-positive cases is given in Table 2B.

Table 2B. HPV-type attribution in HPV-positive cancers other than cervix

Diagnosis	HPV type@								
	HPV α-7 species			HPV α-9 species					other
	HPV-18	HPV-39	HPV-45	HPV-16	HPV-31	HPV-33	HPV-52	HPV-58	HPV-51
VaCa*	5.0%	2.0%	3.6%	58.7%	5.4%	5.0%	3.0%	3.6%	2.3%
VuCa*	4.6%	0.7%	3.3%	72.5%	1.0%	6.5%	1.9%	1.0%	0.0%
AnCa*	3.6%	0.5%	0.9%	80.7%	1.9%	2.7%	0.7%	1.8%	0.0%
PeCa*	1.5%	0.7%	2.7%	68.7%	0.8%	2.9%	1.5%	1.3%	0.9%
OroCa#	1.7%	0.2%	0.4%	86.5%	0.3%	2.3%	0.2%	0.6%	0.0%

@Oncogenic HPV types relevant for HPV vaccination only
*Cases positive for multiple types were attributed proportional to detection in cases with single types
#Attribution by HPV DNA, E6/E7 mRNA, and p16INK4a detection [8]

By combining the etiologic fractions and genotype attributions of the various HPV-related diseases, and projecting those onto their annual incidence, one obtains a proxy of the number of HPV-related diseases that are caused by the relevant types each year {see Tables 3A and 3B}.

Table 3A. Number of cancer cases per year* by HPV type among women in the Netherlands

Diagnosis	HPV type@								
	HPV α-7 species			HPV α-9 species					other
	HPV-18	HPV-39	HPV-45	HPV-16	HPV-31	HPV-33	HPV-52	HPV-58	HPV-51
CIN2	216.8	38.0	68.5	1787.5	570.5	258.6	159.7	144.5	133.1
CIN3	265.0	0.5	70.3	3353.6	389.5	275.9	167.7	243.4	151.5
CxCa	53.4	9.5	28.5	479.1	24.9	41.7	13.9	9.5	10.2
VaCa	1.7	0.7	1.2	19.7	1.8	1.7	1.0	1.2	0.8
VuCa	3.0	0.5	2.2	47.8	0.7	4.3	1.3	0.7	0.0
AnCa	3.5	0.5	0.9	77.5	1.8	2.6	0.7	1.7	0.0
OroCa	0.8	0.1	0.2	39.1	0.1	1.0	0.1	0.3	0.0

*Averaged over the period 2008-2017; absolute incidence figures from IKNL, 2019
@Oncogenic HPV types relevant for HPV vaccination only

Table 3B. Number of cancer cases per year* by HPV type among men in the Netherlands

Diagnosis	HPV type@								
	HPV α-7 species			HPV α-9 species					other
	HPV-18	HPV-39	HPV-45	HPV-16	HPV-31	HPV-33	HPV-52	HPV-58	HPV-51
PeCa	0.7	0.3	1.2	31.6	0.4	1.3	0.7	0.6	0.4
AnCa	3.1	0.4	0.8	68.6	1.6	2.3	0.6	1.5	0.0
OroCa	2.4	0.3	0.6	121.1	0.4	3.2	0.3	0.8	0.0

*Averaged over the period 2008-2017; absolute incidence figures from IKNL, 2019
@Oncogenic HPV types relevant for HPV vaccination only

The direct benefit against cervical disease and other HPV-related cancers for a vaccinated individual was calculated on a cohort basis, as the number of (pre)cancerous diagnoses prevented by HPV vaccination per 100 thousand vaccinated girls or boys. For this purpose, we updated the Bayesian evidence synthesis framework that was previously used to assess the cost-effectiveness of sex-neutral HPV vaccination in the Netherlands [9], but here we only consider the benefit for the vaccinated individual and disregard herd effects.

Type-specific vaccine effectiveness (VE) used in calculations are shown in Table 4. We assumed similar VE against HPV-16 and HPV-18 infections for all vaccines, based on a pooled estimate of 98% in per-protocol populations of the bivalent and quadrivalent vaccine trials with end-points

of HPV-16/18-associated CIN2+ [10]. VE for the other oncogenic HPV types included in HPV9v was based on a combined efficacy against cervical, vulvar, or vaginal disease in a vaccine trial with HPV4v as comparator [11,12]. For HPV4v, we included cross-protection to HPV-31 as stated in the EMA EPAR documentation regarding clinical efficacy against type-specific CIN2+ [13]. For HPV2v, we included cross-protection to HPV-31, -33, -35, -39, -45, and -51, ie. oncogenic types for which significant cross-protection against type-specific CIN2+ has been reported in the EMA EPAR documentation [14]. Cross-protection against (persistent) infection with these types (except HPV-51) has been confirmed in post-vaccine surveillance in the Netherlands, where HPV2v has been used since 2009 [15–18]. In addition, post-vaccine surveillance suggests that cross-protection from 2vHPV extends to HPV-52 and HPV-58 [17], but this was not included in projections of direct benefit against cervical disease and other HPV-related cancers.

For HPV4v, significant cross-protection on a type-specific level in post-vaccine surveillance has been reported for HPV-31 in Norway [19]. In Australia, where HPV4v has been used from the onset, post-vaccination studies have reported a significantly lower prevalence of HPV-31/33/45 combined in vaccinated versus unvaccinated women [20,21], but with HPV-45 still predominating among these types [22]. In the USA, the prevalence of HPV α-9 types, genetically related to HPV-16, decreased significantly among women who received only HPV4v, but the prevalence of HPV α-7 types, genetically related to HPV-18, did not [23]. Luxembourg has offered either HPV2v or HPV4v to (pre)adolescent girls since 2008, and observed significant protection against HPV-31/33/45/52/58 in girls who received HPV2v, but not for girls who received HPV4v [24].

Table 4. Type-specific efficacy against HPV-positive CIN2+ (CIN2/3 or invasive carcinoma)

Vaccine	Efficacy								
	HPV α-7 species			HPV α-9 species					other
	HPV-18	HPV-39	HPV-45	HPV-16	HPV-31	HPV-33	HPV-52	HPV-58	HPV-51
HPV2v	98%	75%	82%	98%	88%	68%	--	--	54%
HPV4v	98%	--	--	98%	56%	--	--	--	--
HPV9v	98%	--	97%	98%	97%	97%	97%	97%	--

Section 2: Direct benefit against cervical disease and other HPV-related cancers for vaccinated girls

In the absence of vaccination, we project an incidence of 701 lifetime cases of invasive cervical cancer, as well as 1,755 CIN2 and 2,834 CIN3

diagnoses from cervical cancer screening, per 100 thousand nine-year-old girls. In addition, we project 38 HPV-related cases of vaginal cancer, 76 of vulvar cancer, 97 of anal cancer and 45 of oropharyngeal cancer.

The direct benefit of each HPV vaccine regarding cervical disease prevention is given in Tables 5a, 5b. HPV9v is expected to provide the highest benefit to vaccinated girls, leading to a projected reduction of 82–86% of CIN2/3 diagnoses and 87% of CxCa cases. For comparison, HPV2v is expected to reduce CIN2/3 diagnoses by 74–78% and CxCa cases by 83%.

Table 5a. Number of CIN2, CIN3 and CxCa cases prevented per 100 thousand vaccinated girls

Vaccine	Diagnosed cases prevented (percentage of total)		
	CIN2*	CIN3*	CxCa
HPV2v	1291 (74%)	2,209 (78%)	583 (83%)
HPV4v	1054 (60%)	1,973 (70%)	514 (73%)
HPV9v	1,444 (82%)	2,441 (86%)	611 (87%)

*Diagnosed cases expected in cervical screening under population-averaged participation rates

Table 4b. HPV-type distribution of cervical cancer cases prevented per 100 thousand vaccinated girls

Vaccine	CxCa cases prevented by HPV-type								
	HPV α-7 species			HPV α-9 species					other
	HPV-18	HPV-39	HPV-45	HPV-16	HPV-31	HPV-33	HPV-52	HPV-58	HPV-51
HPV2v	50	6.8	22	450	21	27	0	0	5
HPV4v	50	0	0	450	13	0	0	0	0
HPV9v	50	0	27	450	23	39	13	9	0

Table 5 gives the direct benefit of each HPV vaccine regarding prevention of vaginal, vulvar, anal and oropharyngeal cancer for vaccinated girls. The relative reductions in cancer incidence for each HPV vaccine are given as a percentage of the total risk for these cancers, irrespective HPV attribution.

Table 5. Number of non-cervical cancer cases prevented per 100 thousand vaccinated girls

Vaccine	Non-cervical cancer cases prevented (percentage of total)			
	VaCa	VuCa	Anca	OroCa
HPV2v	29 (54%)	64 (15%)	84 (77%)	40 (20%)
HPV4v	25 (46%)	58 (14%)	81 (74%)	39 (20%)
HPV9v	31 (59%)	68 (16%)	87 (80%)	40 (20%)

The direct benefit in terms of protection against cervical, vaginal, vulvar, anal and oropharyngeal 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 2018 (Statistics Netherlands) in combination with the age distribution at cancer diagnosis and cancer-specific survival rates over the period 2008–2017 (IKNL, 2019). We corrected for the better prognosis of HPV-induced oropharyngeal cancers relative to HPV-negative oropharyngeal cancers [25]. The number of life-years gained per cancer prevented was estimated at 11.2 years for CxCa, 8.8 years for VaCa, 4.8 years for VuCa, 8.3 years for AnCa, and 7.9 years for OroCa.

As summarized in Table 6, cervical cancer prevention dominates the projected gain in life-years from HPV vaccination for girls vaccinated at nine years of age, although the prevention of non-cervical cancers is expected to contribute substantially. The total gain amounts to 8,110 life-years per 100 thousand girls when vaccinated with HPV2v; 7,231 when vaccinated with HPV4v; and 8,486 when vaccinated with HPV9v. The expected gain in life-years from HPV9v relative to HPV2v is 376 per 100 thousand girls vaccinated at the age of nine years.

Table 6. Number of life-years gained per 100 thousand vaccinated girls

Vaccine	Life-years gained from preventing cancer					
	CxCa	VaCa	VuCa	AnCa	OroCa	TOTAL
HPV2v	6,540	253	306	699	313	8,110
HPV4v	5,761	217	277	670	305	7,231
HPV9v	6,848	274	323	724	317	8,486

Section 3: Direct benefit against HPV-related cancers for vaccinated boys

In the absence of vaccination, we project an incidence of 58 lifetime cases of penile cancer, 90 of anal cancer and 139 of oropharyngeal cancer per 100 thousand nine-year-old boys. The number of life-years lost per cancer detected was estimated at 3.5 years for PeCa, and at 7.1 years both for AnCa and for OroCa (corrected for the better prognosis of HPV-induced oropharyngeal cancers relative to HPV-negative oropharyngeal cancers). Table 7 gives the direct benefit of each HPV vaccine regarding prevention of penile, anal and oropharyngeal cancer for vaccinated boys.

Table 7. Number of HPV-related cancer cases prevented per 100 thousand vaccinated boys

Vaccine	Non-cervical cancer cases prevented (percentage of total)		
	PeCa	Anca	OroCa

HPV2v	43 (24%)	79 (77%)	123 (30%)
HPV4v	40 (22%)	76 (74%)	120 (30%)
HPV9v	45 (25%)	82 (80%)	125 (31%)

The direct benefit in terms of protection against penile, anal and oropharyngeal cancer combined was estimated by calculating the number of life-years gained in a cohort of 100 thousand vaccinated boys. As summarized in Table 8, oropharyngeal cancer prevention dominates the projected gain in life-years from HPV vaccination for boys vaccinated at nine years of age. The total gain amounts to 1,583 life-years per 100 thousand boys when vaccinated with HPV2v; 1,528 when vaccinated with HPV4v; and 1,623 when vaccinated with HPV9v. The expected gain in life-years from HPV9v relative to HPV2v is 40 per 100 thousand boys vaccinated at the age of nine years.

Table 8. Number of life-years gained per 100 thousand vaccinated boys

Vaccine	Life-years gained from preventing cancer			
	PeCa	AnCa	OroCa	TOTAL
HPV2v	150	562	871	1,583
HPV4v	139	540	850	1,528
HPV9v	156	583	885	1,623

Conclusion:
Finally, the expected gain in life-years per vaccinated cohort, consisting of 100 thousand girls plus 100 thousand boys vaccinated at the age of nine years, is given below:

HPV2v: 8,110 + 1,583 = **9,693** life-years gained per vaccinated cohort
HPV4v: 7,231 + 1,528 = **8,759** life-years gained per vaccinated cohort
HPV9v: 8,486 + 1,623 = **10,109** life-years gained per vaccinated cohort

Thus, HPV9v is projected to gain 4.3% more life-years than HPV2v, which is in turn projected to gain 10.7% more life-years than HPV4v.

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