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

HPV vaccination: Background information for the Dutch Health Council

Dit rapport bevat een erratum d.d. 23-03-2018 op de laatste pagina

RIVM Letter report 2017-0020
T.M. Schurink | H.E. de Melker

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Synopsis

HPV vaccination: Background information for the Dutch Health Council

Much (young) sexual active women and men are infected with the human papillomavirus (HPV). Since 2010, 12-year-old girls are vaccinated through the National Immunisation Programme to prevent cervical cancer. Nowadays, we know more about the vaccination; it prevents not only against cancer in the cervix, but also against penile, anal, vaginal and vulvar cancer. In addition, there are also indications for the prevention of oropharyngeal cancers.

In response to those novel insights, the Ministry of Health asked the Health Council to prepare an update of their advice in 2008 to vaccinate all girls in the Netherlands. To support the Health Council, the RIVM has collected and structured relevant national and international information. For example information on the occurrence of HPV infections and HPV-related diseases in girls/women and boys/men as well as the effectiveness and safety of the vaccines.

In the past years, the occurrence of HPV-related cancers in males has steadily increased. Currently, there are three vaccines on the market, which can be used for women as well as for men. In the Netherlands, the bivalent vaccine, protecting against HPV types 16 and 18, is used to date. The other two vaccines protects against more types of HPV. Vaccination coverage among girls is 61 percent. The current programme for girls is expected to lead annually to 350 fewer women with cervical cancer and 100 fewer women who die due to this cancer.

Keywords: human papillomavirus, HPV vaccination, disease burden, vaccine-effectiveness, safety, acceptance, cost-effectiveness

Publiekssamenvatting

HPV-vaccinatie: Achtergrond informatie voor de Gezondheidsraad

Veel (jonge) seksueel actieve vrouwen en mannen zijn geïnfecteerd met het humaan papillomavirus (HPV), dat baarmoederhalskanker veroorzaakt. Sinds 2010 worden 12-jarige meisjes via het Rijksvaccinatieprogramma gevaccineerd om baarmoederhalskanker te voorkomen. Inmiddels weten we meer over deze vaccinatie; zij beschermt niet alleen tegen kanker in de baarmoederhals, maar ook tegen kanker aan penis, anus, vagina en vulva. Ook zijn er aanwijzingen dat het tegen kanker van de mond- en keelholte beschermt.

Naar aanleiding van deze nieuwe inzichten heeft de minister van VWS de Gezondheidsraad gevraagd te bekijken of het advies uit 2008 om meisjes te vaccineren moet worden aangepast.
Om de Gezondheidsraad hierin te ondersteunen heeft het RIVM de relevante informatie uit binnen-en buitenland verzameld en gestructureerd. Het gaat bijvoorbeeld om informatie over de mate waarin HPV-infecties en HPV-gerelateerde ziekten voorkomen bij meisjes/vrouwen en jongens/mannen en over de effectiviteit en veiligheid van de vaccins.

De laatste jaren hebben meer mannen een vorm van kanker gekregen die door het HPV-virus veroorzaakt kan worden. Er zijn drie vaccins tegen HPV op de markt die zowel voor vrouwen als mannen geschikt zijn. In Nederland wordt het vaccin gegeven dat tegen twee typen van het HPV-virus beschermd (HPV-typen 16 en 18). De andere twee vaccins beschermen tegen meerdere typen van het HPV-virus. 61 procent van de meisjes heeft zich laten vaccineren. Door het huidige vaccinatieprogramma zullen per jaar naar schatting 350 minder vrouwen baarmoederhalskanker krijgen en 100 vrouwen minder aan deze vorm van kanker overlijden.

Kernwoorden: humaan papillomavirus, HPV vaccinatie, ziektelast, vaccineffectiviteit, veiligheid, acceptatie, kosteneffectiviteit

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Preface

This report provides background information on human papillomavirus (HPV) and focuses particularly on knowledge and data that have become available after the 2008 Health Council recommendation regarding HPV vaccination [1]. At that time, the Health Council recommended the introduction of HPV vaccination for girls aged 12 in order to prevent cases and deaths from cervical cancer. In 2010, the routine HPV vaccination of girls 12 years old was introduced in the Netherlands (for girls born in 1997 or later). In 2009, a catch-up campaign was carried out for girls born in the period 1993-1996. The bivalent vaccine, which covers HPV types 16 and 18, has been used up to the present date. The vaccination coverage in the catch-up campaign was 52.3%. At present, the vaccination coverage in the routine vaccination programme for girls amounts to 61.0%.

Since the last Health Council recommendation was issued, important novel insights on the epidemiology, virology and immunology of HPV infections have become available, especially knowledge about HPV-related diseases other than cervical cancer. Currently, three vaccines are available to prevent HPV-related diseases, i.e. a bivalent vaccine (against types 16 and 18), a quadrivalent vaccine (against types 6, 11, 16 and 18) and a nonavalent vaccine (against types 6, 11, 16, 18, 31, 33, 45, 52 and 58).
For this reason, the Ministry of Health asked the Health Council to prepare an update of their recommendation. In this report, national and international information on HPV-related diseases and HPV vaccination is provided. The document is structured by the criteria defined by the Health Council for the evaluation of vaccines.

1 Human papillomavirus disease

Summary

Human papillomavirus (HPV) infection is common in (young) sexually active women and men. Most HPV infections are cleared within 2 years. When an infection with a high-risk HPV (hrHPV) type persists, this can lead to the development of (precursor lesions of) cancer. Cervical cancer is the most prevalent of these, but persistent hrHPV infection at other anatomic sites can lead to penile, anal, oropharyngeal, vaginal and vulvar cancer. Most HPV-related cancer cases are caused by hrHPV types 16 and 18. Infection with low risk types of HPV (mostly HPV types 6 and 11) can give rise to genital warts.

In the Netherlands, pre-vaccination cervical hrHPV prevalence was highest among female sexually transmitted infections (STI) clinic visitors (58%). The lowest cervical hrHPV prevalence (3%) was found among girls 14-16 years of age, who were eligible for the catch-up vaccination. In male heterosexual STI clinic visitors (16-24 years), hrHPV prevalence in penile samples was about 40%. For men who have sex with women, anal DNA prevalence was rare (overall HPV 4%). Among men who have sex with men (MSM), hrHPV prevalence varied by anatomical site (anal, penile and oral) and presence of HIV-infection with the highest prevalence at the anal site and in HIV-infected men (65%).

In the Netherlands, about 700 women are diagnosed with cervical cancer annually and approximately 50, 300-400, 140 and 200 individuals are annually diagnosed with vaginal, vulvar, penile and anal cancer, respectively. Genital warts are diagnosed in 2,000 STI-attendants and in nearly 38,000 GP visitors. Recurrent respiratory papillomatosis (RRP) is a rare syndrome of recurring proliferations of multiple papillomas in the respiratory tract. The prevalence of laryngeal papillomatosis is estimated at 4-7 per 100,000.
The disease burden due to HPV infection is generally computed using the disability-adjusted life-year (DALY) measure, which integrates morbidity and mortality to quantify health burden for the total population. In the Netherlands in 2011-2014, a disease burden of 10,600 DALYs per year in females and 3,346 DALYs per year in males has been estimated. During the period 1989-2014, the burden of cancers other than cervical cancer has steadily increased, especially in males. In 2014, the male share of the total disease burden reached 26%.

1.1 HPV and infection

1.1.1 Pathogen

Human papillomavirus (HPV) is a non-enveloped, double-stranded, circular DNA virus belonging to the Papillomaviridae (PV) family. Papillomaviruses contain a stable DNA genome that is replicated with high fidelity by host cell machinery [2]. The HPV genome is surrounded by a capsid composed of two proteins; L1 is the major capsid protein and L2 is the minor capsid protein.
Over 170 different HPV types based on DNA sequencing have been identified to date and this number is increasing thanks to modern virus

identification and sequencing techniques [3]. HPV types belong to five different genera (alpha, beta, gamma, mu and nu) within the PV family. The genome organization of most viral genotypes is similar, comprising a circular DNA genome of approximately 7,900 bp with three functional coding regions: 1. a region coding for early viral function (E), representing genes involved in the viral genome regulation, replication and modification of host processes; 2. a region of late viral function (L) encoding capsid proteins; 3. a long control region (LCR), which contains promotor elements and transcription factor binding sites. Eight HPV genes (E1, E2, E4, E5, E6, E7, L1, L2) are transcribed from the same DNA strand as two transcripts and are processed to yield different gene products [4]. In short, E1 and E2 aid in viral replication. E2 is also involved in regulating expression of E6 and E7, which are the main oncogenes, primarily functioning as downregulators of human p53 and pRB, respectively. E4 is involved in virion release upon maturation. E5 has been associated with immune evasion and the stimulation of cell growth. The late genes L1 and L2 form the virion capsid. Immune response against the virus is mainly caused by the virion capsid, consisting of major and minor capsid proteins L1 and L2 [4].

Only HPVs belonging to the alpha genus are known to cause mucosal pathology, which can lead to cancer. The alpha genus is further stratified in 13 species, each containing a number of genotypes [5]. Within the alpha-HPV genus, a distinction is made between HPV genotypes that are able and unable to cause high-grade cervical disease, the so-called high-risk (hr) and low-risk (lr) HPV types. Thirteen types of HPV are currently considered to be hrHPV types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) [6].

By definition, HPV types differ from each other by at least 10% in the highly conserved L1 (major capsid protein) gene sequence. Within HPV types, variant lineages can be distinguished when the nucleotide sequences of the L1 open reading frame (ORF) differ by less than 10%, differences of 0.5-1% are designated as sublineages [7]. For example, HPV16 can be divided into four main variant lineages (A, B, C, D) and nine sublineages. Variants of HPV16 have been shown to influence persistence, the progression to pre-cancer and the development of cancer [7]. Furthermore, specific HPV16 variants are found to be associated with geography and ethnicity, and the risk of specific HPV16 variants persisting and progressing to (pre) cancer varies by a woman's ethnicity [8]. Similarly, for HPV18 intratypic variants occur naturally (A, B and C), but the evidence for differences in persistence or progression to (pre) cancer is less clear. Similar to HPV16, geographic associations for variants can be seen for HPV 18 as well. For example, lineage A variants for both HPV16 and -18 have been found at highest frequencies in the Western population [7].

Recently, the intratypic diversity was determined for HPV16 and HPV18 viruses found in the Netherlands among 16 to 24-year-old STI-clinic visitors before the introduction of vaccination [9]. The most frequently identified variants in the Dutch isolates for HPV16 and HPV18 were lineage A variants. Non-A variants of HPV16 and HPV18 were found at low frequencies, 7% and 14% respectively. In addition, non-A variants

of HPV18 were found more frequently in persons with a self-reported non-European ethnicity [9].

Since the introduction of HPV vaccination with the bivalent vaccine in the Netherlands in 2009, CIb/RIVM has monitored the occurrence of HPV types circulating in adolescents and young adults in the Netherlands, in order to obtain insight into the prevalence of HPV types in the (vaccinated) population (see Section 2.3.4.2).

1.1.2 Natural history of infection

HPV infection is common in (young) sexually active women and men. An HPV infection generally resolves spontaneously within two years, with clearance of viral presence [10]. In some cases, particularly with hrHPV, infections persist, causing lesions that can progress to cancer.

Over the past several decades, research has focused primarily on HPVs in relation to cervical cancers.
Several papers have been published describing the natural history of HPV infection, gene expression and transformation in detail for cervix [11-14]. HPV can reach its niche environment via micro-abrasions in the cervical mucosa that expose the basal cell layer. Development of the virus occurs in parallel with the differentiation of the host cell, which aids in the initial avoidance of the host immune system. When hrHPV infections persist, this can cause histopathologically distinct stages of intraepithelial lesions such as cervical intraepithelial neoplasia, (CIN1-3) [15]. Development from initial infection to cancer may take several decades [16]. HPV infection can be contracted through sexual intercourse with an infected partner, resulting in the initial infection in basal cell layer (Figure 1.1.1). In these cells, viral genomes are maintained as episomes (extra chromosomal elements) that replicate in concert with cellular replication [17]. As cells differentiate, a high level of replication of viral genomes (episomes) is induced, concurrently with the synthesis of capsid proteins, followed by virion assembly. Approximately 60% of these infections will induce (type-specific) seroconversion (positive antibodies against the specific HPV type) and may be associated with mild abnormalities (such as CIN1) [18]. If an infection is not cleared, but rather persists, and HPV viral DNA remains present, this may become integrated into host chromosomes. Host integration of viral DNA leads to an increased risk of progression to true cervical cancer precursor lesions (e.g. CIN3). These lesions can still regress into normal tissue but are more likely to progress to cancer over a period of several years when left untreated [18]. Infections with HPV16 are most likely to persist and progress to pre-cancerous and cancerous lesions [19]. Moreover, the risk of developing CIN lesions is increased by the presence of coinfections with other HPV types [19].

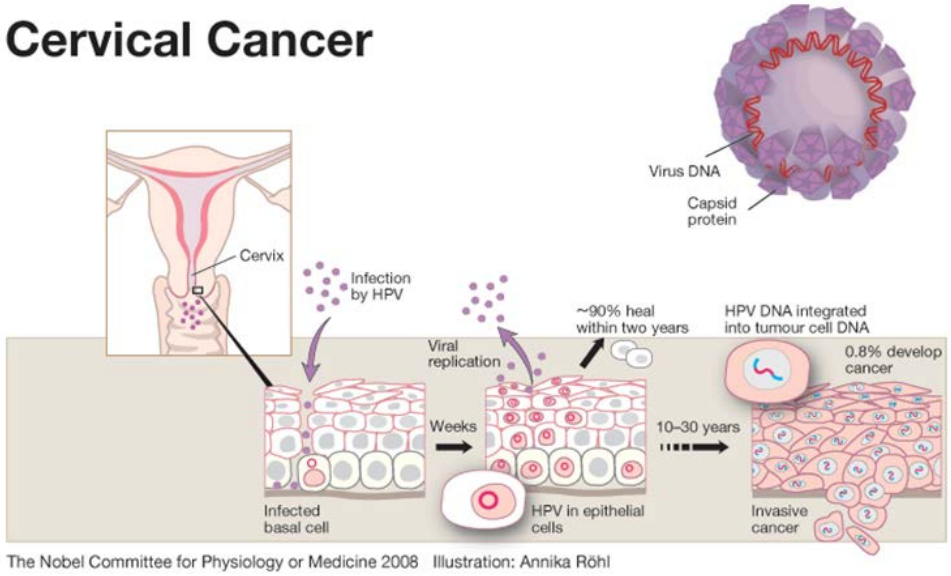

Figure 1.1.1 Natural history of an HPV infection in the cervix
This figure shows the processes from HPV infection to cancer in the cervix. HPV infects the basal cells that become exposed by trauma or wounding. Viral replication starts after a few weeks. Viral DNA is maintained as the cells differentiate and move towards the epithelial surface. At the epithelial surface, cells die and are removed from the body by natural processes. Large amounts of virus are released from the epithelial surface for transmission. Most HPV infections will be cleared within two years. If the immune system is not able to clear the HPV, HPV DNA can become integrated in host cell genome and lead to deregulation of the cell and carcinogenic progression.

Recently there has been growing interest in understanding the relation between HPV infection and other cancers in men and women that may occur at multiple anatomic sites (penile, anal, oropharyngeal, cervical, vaginal and vulvar) (Figure 1.1.2). Differences in HPV natural history by gender and anatomic site have been observed [20]. Infections with hrHPV types in the anal canal seem to progress similar to an infection in the cervix. These infections can cause histopathologically distinct stages of anal intraepithelial neoplasia (AIN 1-3) lesions, which can progress to anal cancer. Penile infections in men occur, but are less persistent than anal infections because the infection of the keratinized epithelium of male genitals may clear more rapidly compared with the mucosal epithelium of the anus [21]. Head and neck cancers are also related to HPV infections, particularly oropharyngeal carcinoma in tonsils and the base of the tongue. More than 50% of these tumours test positive for HPV16 [22]. Due to the nature of the tonsillar crypt, epithelium in the oropharynx, direct access of the virus to the basal layer is allowed. The HPV virus enters the basal cell layer and the life cycle of hrHPVs (a productive viral life cycle) can start. The virus can also persist with minimal viral gene expression and without detection by a host's immune system, leading to the development of invasive carcinomas [22, 23]. The true attributable fraction of HPV in vulvar cancer remains unclear. A subset of vulvar carcinomas is preceded by a premalignant disease of the lower genital tract, vulvar intraepithelial neoplasia (VIN), three grades of which are identified (VIN 1-3). For this type of vulvar carcinoma, infection with hrHPV is an early event in a multistep process of vulvar carcinogenesis and HPV integration into host cell genome seems to be related to the progression of vulvar dysplasia [24]. It has

become increasingly evident that HPV activity or HPV transformation is necessary in order to define true HPV-driven tumours outside the cervix. A recent article of Halec et al. [25] describes evidence for HPV transcriptional activity in vulvar cancer tissues. Vaginal intraepithelial neoplasia (VAIN) is a premalignant lesion, potentially leading to vaginal cancer. Similar to other anatomic sites, as described, there are three grades of VAIN (1-3). There is little understanding about the natural course of VAIN and its capacity to progress or regress. Furthermore, there is controversial data about the HPV detection rate in VAIN lesions. Lamos et al. [26] state that HPV16 is the main virus-type to be associated with the development of VAIN.

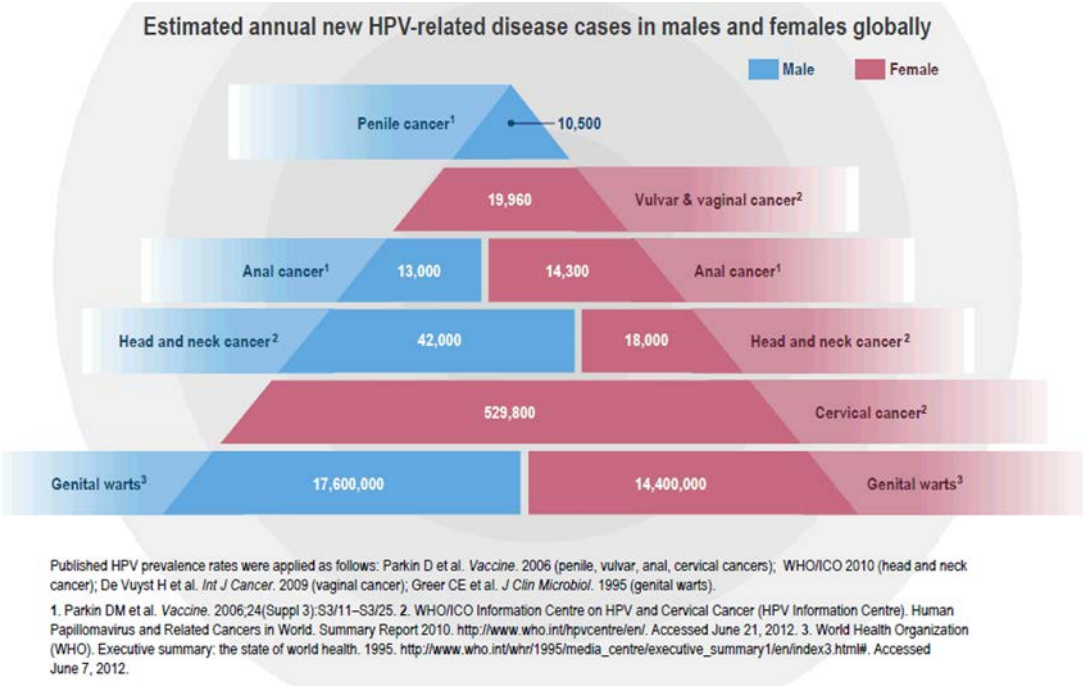

Figure 1.1.2 Estimated annual new HPV-related disease cases in males and females globally
From A. Guilliano [27]

Several biomarkers have been found to be associated with the progression of HPV infection towards disease states, such as viral load [28-30], DNA methylation [14, 31], overexpression of viral E4, E6 and E7 or of host p16 and pKi67 [32-34]. However, overlap in the various markers between disease states limits their predictive value. So far, research has primarily focused on biomarkers for the sake of clinical guidance, while the applicability of biomarkers for epidemiological purposes has been lower.

1.1.3 HPV infection epidemiology

Genital infection with HPV is the most common sexually transmitted infection. The lifetime risk of cervical HPV infection was estimated at around 80% in a Finnish population in the 1980s [35]. In the Netherlands, lifetime risk for HPV16 infection has been estimated at 46% and for HPV18 at 40% [36]. Most available prevalence data are for women. With respect to men, more and more data are becoming available, but prevalence has not been studied as extensively [37].

Several measurements taken during the natural course of HPV infection are being used to describe the epidemiology (Figure 1.1.3). Acquiring a new infection is measured as the transition from HPV DNA negative to positive at a certain time point. This is referred to as the incidence. Prevalence is considered as the percentage of HPV DNA positives at a specific time point. HPV DNA positivity can transit towards negativity as a result of clearance of the infection. Yet another possibility may be that the virus has become latent and is therefore not picked up any longer by the test, but has not been cleared [18]. If HPV DNA positivity of the same HPV type persists between time points in epidemiological studies, the term persistence is used. The interval between consecutive measurements varies between studies [10]; i.e. two positive test results with an identical HPV type at months 0 and month 12 (or 6 months etc.). For the interpretation of study results, one should be aware of the differences in definition criteria used in the various studies.

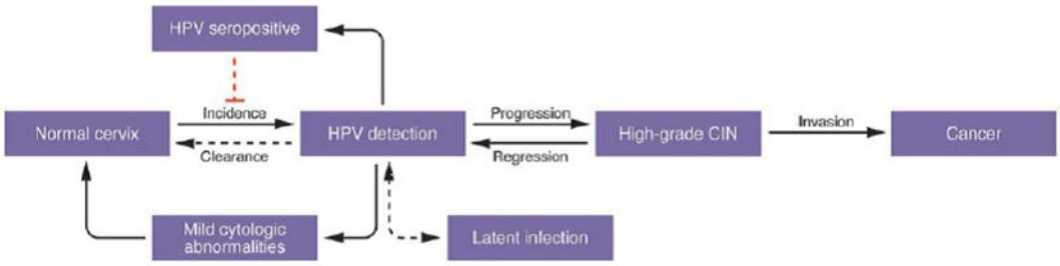

Figure 1.1.3 Natural course of HPV infection and cervical cancer.
From Gravitt, 2011 [18]
CIN = cervical intraepithelial lesions

1.1.3.1 Females

Worldwide, the (adjusted) cervical HPV prevalence among women without abnormalities in cervical cytology smears amounts to 11.7% (95% CI 11.6-11.7%), with the oncogenic types HPV 16, 18, 31, 39, 51, 52, 56 and 58 being the most prevalent types [38] (Figure 1.1.4).

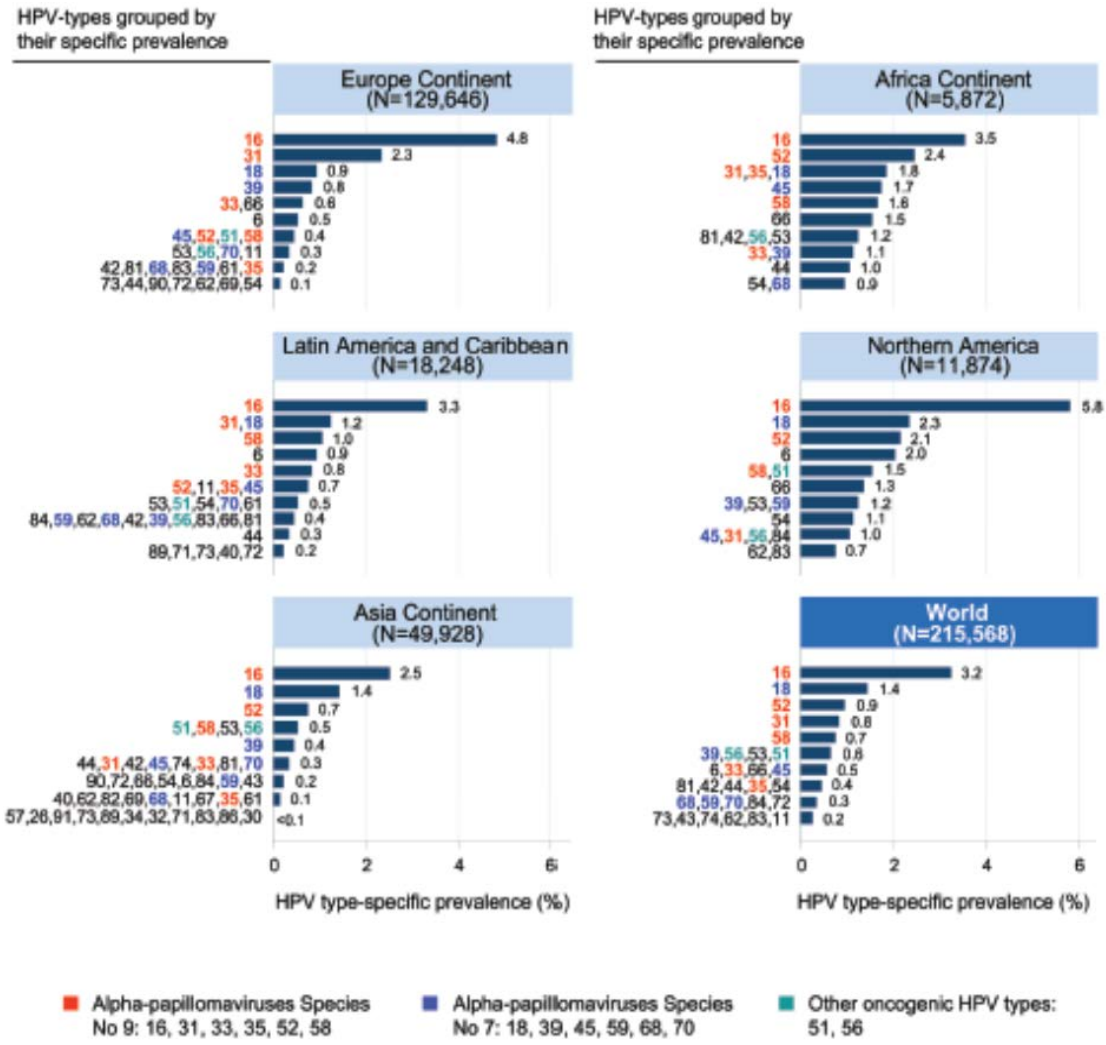

Figure 1.1.4 Type-specific human papillomavirus (HPV) prevalence in women with normal cytology for most frequent HPV types by geographical region
From Bruni et al. 2010 [38]

In a cohort from Arizona, the incidence of cervical infections with any HPV type was estimated at 35.3 (95% CI 24.7-48.8) per 100 person-years (PY). Median time to clearance for hrHPV was estimated at 9.8 months [39].

In the Costa Rica Vaccine Trial (CVT), the prevalence of HPV16/18 at the cervical, anal and oral sites was examined at the four-year follow-up visit of both the vaccinated group and the control group (Hepatitis A vaccine). Women aged 18 to 25 were randomly assigned to either the bivalent HPV vaccine or the control group. Anal specimens were collected in sexually active women. In the full cohort (all women consented to cervical, anal and oral samples and with HPV DNA test results available). Among the unvaccinated women, cervical HPV16/18 prevalence was 8.1%, anal HPV16/18 prevalence was 5.9% and the oral HPV16/18 prevalence was 0.4%. In the HPV naïve cohort (excluded women seropositive for HPV16/18 or high-risk cervical HPV DNA+ at baseline or LEEP during vaccination phase) the prevalence were 7.8% for HPV16/18 at the cervix and 4.8% at the anus [40].

In a multi-ethnic cohort in Hawaii (between 1998-2003), which was initiated with the aim of identifying determinants for persistent cervical HPV infections, participants were asked to optionally collect an anal specimen. Overall, 27% of women were positive for anal HPV DNA, compared with 29% for cervical HPV DNA. A high concordance in HPV types was found for women with both a cervical and anal HPV infection [41]. From this cohort, 650 women were followed longitudinally. At enrolment, anal HPV prevalence was 42%. The anal hrHPV incidence was 19.5 (95% CI 16.0-23.6) per 1,000 person-months (PM) [42]. The median duration for the clearance of anal HPV infections was estimated at 150 days. Median duration for the clearance of HPV16 and HPV18 was 132 days and 212 days, respectively [43]. Mosiciki et al. found slower clearance of HPV16 compared with other hrHPV types HPV56, HPV-66 and a trend for HPV-39. All the other types (18, 51, 52, 53, and 59) cleared at similar rates to HPV16 [44].

Among university students using physician-collected swabs, the incidence rate for vulvovaginal HPV infection was estimated at 16.0 per 100 PY. For comparison, the incidence rate of cervical infections in this study was 12.7 per 100 PY [39].

1.1.3.2 Males

Like in females, HPV genital occurrence in males is very common. A Finnish study comparing male genital infection with female cervical infection data at baseline and 7 years later among pregnant women and their male partners showed an incidence for any HPV type of 32.3% (95% CI 16.7-51.4%) and 16.7% (95% CI 6.4-32.8%) respectively [45]. Although the long interval between measurements might have complicated the interpretation of these findings, as incidence followed by clearance within the interval might have been missed. As in females, HPV prevalence in males varies substantially among regions and risk groups, but variation between age groups is less pronounced among males than among females [46]. A systematic review including studies performed between 1985-2008 estimated that among European males the genital (swabs from male genital area, including urethra, glans, shaft, scrotum and perineum) HPV prevalence was 12.4% in the general male population (age range 16-79) and 30.9% for the high-risk population (STI clinic attendees, HIV+ males or male sexual partners of women with an HPV infection or abnormal cytology; age range 15-87), with HPV16 and HPV18 being the most prevalent HPV types [47]. An Italian study conducted among male visitors to an STI clinic without overt signs of a previous HPV infection estimated a periurethral HPV DNA prevalence of 49%. Anal and oral prevalence was found in, respectively, 43% and 37% of participating men [48].

A recent systematic review [39] described that penile hrHPV incidence was found to be higher in HIV+ men than in HIV- men in Africa, ranging from 42.0 to 72.9 per 100 person-years and from 19.7 to 32.9 per 100 PY, respectively. A higher incidence for HPV was also found among HIV+ MSM in Spain than among HIV- MSM, 11.6 versus 5.1 per 100 PY, respectively. The highest type-specific incidence was found for HPV16. HPV16 and HPV52 take the longest time to clear in circumcised men, while the same is the case for HPV52 and HPV58 in uncircumcised men. The median time for clearance in HIV- men was higher for HPV16 (12.2

months) than for HPV18 (6.3 months). For HIV+ men, this was 27.8 and 35.3 months, respectively. Persistence of hrHPV at 6 and 12 months, respectively, was found in 31% and 25% of HIV- and 43% and 28% of HIV+ men.

This review (it should be noted that this might not reflect the general population) also summarizes the epidemiology of male genital HPV infection at different sites, such as the penis/urethra, coronal sulcus, glans, shaft, scrotum, balano-preputial groove, urinary meatus. Incidence of any HPV ranged from 14.8 to 50.5 per 100 PY for different adult study populations. Among university students, the incidence was even higher at 62.4%. Among male partners of pregnant women, incidence was 32.3%. The most prevalent HPV type was HPV16 in all included studies. The highest incidence for HPV was observed in the oldest age group studied (41-44 years), while the highest incidence of hrHPV was found in men 26-30 years of age. The median duration of an incident male genital HPV infection varied between 5.1 and 7.1 months. For HPV16/18 this varied between 5.4 and 11.1 months [39].

The incidence of anal HPV infections was found to be lowest in men who have sex with females and HIV+ men who have sex with females, respectively 9.7 and 7.9 per 100 PY; while for men who have sex with men (MSM) and HIV+ males (gender of partner not specified) the incidence ranged from 21.3-46.2 per 100 PY.
Among MSM, HPV16/18 showed the highest incidence. For prevalent anal HPV infections, the clearance rate varied between 14.6 and 66.7 per 100 PY depending on HPV type. The time to clear an HPV16 or HPV18 infection ranged between 30 and 39.5 months. Persistence of anal hrHPV infections for 6 months occurred in 51.0% of men who have sex with women and 24.2% of MSM [39].

Oral HPV infections showed an incidence rate in HIV- and HIV+ men of 6.7 and 5.7-6.1 per 100 PY, respectively. Among university students, oral incidence was 12.3% over one year. HPV16 was the most identified HPV type in oral incident infections. No difference in the incidence rates of hrHPV types in oral infections was found across age groups among HIV- men [39].

1.1.3.3 Dutch Females

The HPV prevalence, independent of HPV type, in cervico-vaginal self-swab samples taken from the Netherlands (in unvaccinated women aged between 14 and 35 years) measured since 2006 varied between 4% and 72%, mainly depending on age, risk profile (e.g. years since sexual debut and number of sexual partners) and ethnicity. Lenselink et al. [49] found that increasing age, current smoking behaviour, the number of partners in the past six months and the years of being sexually active were significantly associated with HPV prevalence. Mollers et al. observed that increasing age, younger age of sexual debut, a higher number of lifetime sexual partners and a higher age of the partner were risk factors for hrHPV prevalence [50]. Vriend et al. found that genital HPV DNA prevalence was associated with genital chlamydia, as anal HPV DNA prevalence was associated with anal chlamydia [51]. Different estimates for overall and hrHPV genital prevalence in the Netherlands are shown in Table 1.1.1. Overall HPV prevalence was highest among

female STI-clinic visitors. The lowest prevalence was found in girls 14-16 years of age, who were eligible for the catch-up vaccination.

Table 1.1.1 Overall and hrHPV genital prevalence estimates (vaginal self-swabs) in unvaccinated women for the Netherlands. In all studies HPV DNA detection was done by the use of the SPF10-DEIA LiPA25.

Reference	Study population	Study period	Age (years)	N	Overall HPV prevalence (95% CI)	hrHPV prevalence (95% CI)
Alberts 2016 [52]	Participants from seven ethnicities (HELIUS-study) living in Amsterdam	2011-2013	18-34	592	40%	29%
	Dutch			108	53%	42%
	South-Asian/Surinamese			100	29%	18%
	African Surinamese			111	50%	32%
	Ghanaian			81	37%	26%
	Moroccan			103	33%	26%
	Turkish			89	36%	29%
Lenselink 2008 [49]	Unscreened women for the general population	2006	18-29	2,065	19.0%	11.8%
Mollers 2012 [50]	Girls eligible for the catch-up vaccination	2009	14-16	1,800	4%	3%
Mollers 2013 [53]	Female participants of the CSI-study	2009	16-29	3,282	53.9% (52.5-55.6%)	41.9% (40.2-43.6%)
		2009-2010		2,014	61.9% (50.8-64.0%)	48.0% (45.8-50.2%)
Schmeink 2013 [54]	Unscreened women for the general population	2006-2007	18-29	2,065		12.3%
Vriend 2012 [55]	Heterosexual female STI clinic visitors	2009	16-24	1,136	71.8% (69.1-74.4%)	58.2% (55.3-61.0%)

*CI = confidence interval; CSI = Chlamydia Screening Intervention; STI = sexually transmitted infection.
As part of the CSI programme in the Netherlands, a prospective study among 16 to 29-year-old women and men was conducted. All sexually active men and women from Amsterdam, Rotterdam and a specific part of South Limburg in these age groups were invited to enrol in this study. Participants from South Limburg were selected according to a risk profile. In samples of women that gave additional consent for testing for other STIs, HPV was also examined.

Type-specific HPV DNA prevalence for HPV types included in the bivalent, quadrivalent and/or nonavalent vaccine are described in Table 1.1.2 [49-55]. HPV16 and HPV18 prevalence were generally the most prevalent HPV types among unvaccinated women.

Table 1.1.2 Type-specific HPV DNA prevalence (vaginal self-swabs) among unvaccinated women for HPV types included in the three prophylactic HPV vaccines. In all studies HPV DNA detection was done by the use of the SPF10-DEIA LiPA25.

Study		Study period	HPV 6	HPV 11	HPV 16	HPV 18	HPV 31	HPV 33	HPV 45	HPV 52	HPV 58
Alberts 2016[52]	Participants from seven ethnicities (HELIUS-study)	2011-2013	3%	0%	6%	4%	5%	1%	2%	8%	2%
	Dutch		3%	0%	6%	10%	10%	4%	4%	13%	2%
	South-Asian/ Surinamese		4%	0%	4%	4%	2%	0%	1%	4%	4%
	African Surinamese		5%	0%	5%	3%	5%	2%	3%	9%	4%
	Ghanaian		1%	0%	4%	0%	2%	1%	1%	7%	0%
	Moroccan		4%	1%	6%	2%	5%	0%	2%	5%	0%
	Turkish		2%	1%	13%	3%	3%	0%	0%	9%	0%
Mollers 2013 [53]		2009-2010		5.8%	10.8%	4.2%	7.2%^	*	7.2%^	*	*
				5.9%	11.7%	4.6%	7.3%^	*	7.3%^	*	*
Lenselink 2008 [49]		2006	0.6%	0.2%	2.8%	1.4%	*	*	*	2.5%	*
Mollers 2012 [50]		2009	*	*	*	*	*	*	*	*	*
Schmeink 2013 [54]		2007-2010	0.6%	0.2%	2.8%	1.5%	1.5%	0.9%	0.1%	2.5%	0.3%
Vriend 2012 [55]		2009	*	*		22.5%	*	*	*	*	*
Vriend 2013 [51]		2009/2011	*	*	17%	*	*	*	*	*	*

* = See figure in original article
^ = Combined for HPV31/45

Schmeink et al. described an incidence rate for hrHPV of 17.0 per 1,000 PY (95% CI 15.3-18.9%) among 18 to 29-year-old Dutch women recruited through advertisement and active recruitment sites. The HPV types with the highest incidence rates were HPV 16, 52, 51, 31 and 18 [54]. Among some of the 16 to 29-year-old female participants in the Chlamydia Screening Intervention (CSI) study, HPV prevalence (vaginal self-swab) was also determined in 2009 and 2010. This study originally included sexually active males and females 18-29 years of age. An incidence of any HPV type of 45.3% (95% CI 43.1-47.5%) was reported, which persisted for at least one year in 59.2% (95% CI 56.4-62.1%). For hrHPV (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59), this was 31.7% (95% CI 29.6-33.7%) and 44.7% (95% CI 41.8-47.6%), respectively [53]. The most frequent HPV types were 16, 31, 51, 52 and 66. The overall HPV incidence rates varied strongly between chlamydia positive and chlamydia negative women, at 63.6% (95% CI 51.6-74.2%) and 36.5% (95% CI 34.4-38.7%), respectively. The most prevalent HPV types for persistent infections were 16, 31, 33, 35 and 45. For persistent infections, the differences between chlamydia positive women and chlamydia negative women were less clear and consistent, respectively 58.3% (95% CI 44.3-71.2%) and 58.1% (95% CI 55.0-61.2%) [56].
To monitor possible changes in HPV dynamics over time, a biennial cross-sectional study among 16 to 24 year-old male and female STI-clinic attendees (PASSYON) was set up [55]. Some of the female participants also provided anal samples in 2009 and 2011 (n=118). Of these, 32% were positive for any HPV DNA [51].

Data on the epidemiology of oral HPV presence among women in the Netherlands were not found.

1.1.3.4 Dutch heterosexual males

Data on HPV prevalence in heterosexual males in the Netherlands are scarce. In heterosexual male visitors to STI-clinics between 16 and 24 years of age, measured in 2009, Vriend et al. found an overall HPV prevalence of 53.7% (95% CI 49.0-58.4%) and an hrHPV prevalence of 39.5% (95% CI 35.0-44.2%) in penile samples. For HPV types 16/18, prevalence was 16.3% [55]. For men who have sex with women, anal DNA prevalence was rare (4%) [51]. The most prevalent hrHPV type in penile samples was HPV51 and in anal samples it was HPV16 and HPV18 [51, 55].

Data on the epidemiology of oral HPV presence among heterosexual men in the Netherlands were not found.

1.1.3.5 Dutch men who have sex with men (MSM)

An overview of Dutch studies that examine HPV DNA prevalence among unvaccinated MSM is shown in Table 1.1.3. The available data for MSM in the Netherlands mostly derive from the HIV & HPV in MSM (H2M) study, i.e. a cohort study executed in 2010/2011 among HIV+ and HIV- MSM that were 18 or older and were recruited in Amsterdam [57-60].

Table 1.1.3 Overall HPV prevalence estimates in MSM in the Netherlands

Reference	Study population	Anatomic site	Study period	Age (yrs)	N	Overall HPV prevalence (95% CI)	hrHPV prevalence* (95% CI)
Vriend 2013 [51]	MSM STI clinic visitors	Anal	2009/2011	16-24	124	33%	
		Penile			173	16%	
van Aar 2013 [61]	Participants in the H2M study (Amsterdam)		2010-2011	>18			
	HIV+	Anal			317	78.2% (73.3-82.7%)	64.7% (59.1-69.9%)
		Penile			317	49.5% (43.9-55.2%)	32.2% (27.1-37.6%)
	HIV-	Anal			459	60.4 % (55.7-64.9%)	45.1% (40.5-49.8%)
		Penile			460	29.6% (25.4-34.0%)	16.3% (13.0-20.0%)
Mooij 2013 [58]	Participants in the H2M study (Amsterdam)		2010-2011	>18			
	HIV+	Oral			276	56.7% (51.2-62.2%)	24.8% (20.0-29.6%)
	HIV-	Oral			413	27.6% (23.5-31.7%)	8.8% (6.2-11.5%)
Van Rijn 2014 [60]	Participants in the H2M study (Amsterdam)		2010-2011	>18			*genotypes 16, 18, 31, 33, 45, 52, 58*
	HIV+	Anal			306		56.9%*
		Penile			306		23.2%*
		Oral			306		17.3%*
	HIV-	Anal			441		33.6%*
		Penile			441		11.1%*
		Oral			441		4.3%*

CI = confidence interval; H2M = HPV and HIV in MSM study; HIV = human immunodeficiency virus; MSM = men who have sex with men; STI = sexually transmitted infections.
*The paper by van Rijn et al. 2014 describes only prevalence against HPV types 16, 18, 31, 33, 45, 52 and 58.

Type-specific HPV DNA prevalence in MSM varied by anatomical site and HIV-infection, but in general HPV16 was the most prevalent HPV type [51, 58, 60, 61].
Type-specific hrHPV incidence rates for HIV- MSM varied between 1.6 and 8.3 per 1,000 PY in anal hrHPV infections and between 0.6 and 4.5 per 1,000 PY in penile hrHPV infections, depending on HPV type with HPV51 and HPV52 most frequent for anal infections and HPV16 and HPV51 for penile infections. For HIV+ MSM, incidence rates varied between 2.6 and 12.4 per 1,000 PY for anal infections and between 1.1 and 6.6 per 1,000 PY for penile infections, with HPV31 and HPV52 most frequent for anal infections and HPV16 and HPV51 for penile infections. Type-specific incidence rates were significantly higher in HIV+ MSM than they were in HIV- MSM for HPV types 16, 31, 35, 52, and 56 in anal hrHPV infections and for HPV types 31 and 35 in penile hrHPV infections [62].

Among the HIV- MSM risk factors for anal hrHPV infections are a higher number of anal sex partners in the past six months and a higher number of lifetime male sex partners. For HIV+ MSM, these risk factors include being younger, having receptive anal intercourse in the past six months and having a higher nadir (lowest ever) CD4 cell count. A higher number of lifetime male sexual partners was significantly associated with penile hrHPV infection in HIV- MSM. A detectable HIV viral load was found to be a risk factor for penile hrHPV infections among HIV+ MSM [61].

In the H2M study, the prevalence of oral hrHPV infection in MSM was associated with HIV infection and increasing age [58]. The six-month incidence of oral hrHPV infection was 14.1% (95% CI 10.2–18.8) in HIV+ MSM and 4.1% (95% CI 2.4–6.5) in HIV- MSM [57]. At a median follow-up time of twelve months, type specific oral HPV infection incidence ranged between 0.2 and 1.1 per 1,000 PM for HIV- MSM and between 1.3 and 3.5 per 1,000 PM for HIV+ MSM [59]. HIV infection and recent use of cannabis were associated with oral hrHPV infection incidence at six months, and HIV infection and a higher number of recent oral sex partners was associated with oral hrHPV infection incidence at twelve months [57, 59]. The distribution of oral hrHPV types differed from that found in anal and penile samples, for example in HIV+ MSM, HPV33 was more often detected in oral samples than in anal and penile samples (24% vs. 12% and 10%, respectively) and in HPV MSM, HPV16 was detected more frequently in oral samples than in anal and penile samples (43% vs. 29% and 31%, respectively) [60].

1.1.3.6 HPV-serology in the Netherlands

1.1.3.6.1 HPV-antibody response

HPV antibodies are less frequently observed following transient infections compared with persistent infections. Nonetheless, not all people with a persistent infection seroconvert [63]. During infection, many viral particles are produced which are shed when differentiating cells reach the surface (productive infection). In this process, there is no cytolysis or necrosis and subsequently no inflammation. In addition, there is no viremia in the HPV life cycle and only very low levels of viral protein are presented to the immune system of the host. As a result, HPV is effective in evading detection by the immune system for long periods and generates only a weak immune response. The absence of

detectable antibody levels therefore does not exclude past exposure to HPV. A detectable antibody response against the HPV L1-capsid protein is established in 50-70% of infected individuals, also called seroconversion. As naturally induced HPV-specific antibodies persist in the blood for a relatively long time, they can be considered a measure of both ongoing and previous HPV infections. Unfortunately, it is unclear whether and how levels of naturally derived antibodies correlate with protection against re-infection with HPV [63, 64].
Serological assays can monitor (naturally infected or vaccine-derived) HPV-specific antibodies. This can provide information on the immunogenicity of the HPV vaccine, although no correlate of protection for vaccinated individuals has been established yet.

1.1.3.6.2 Available serological assays

Several serological assays have been developed, among which the pseudovirion-based neutralization assay (PBNA) is considered to be the golden standard. The PBNA measures the full spectrum of neutralizing antibodies, but this technique is very labour intensive and therefore difficult to use in large epidemiological studies. An automated pseudoviron-based HPV neutralization assay has been developed that is well-suited for high-throughput screening [65]. Other available serological assays are used as alternatives to the PBNA. The most commonly used is the virus-like-particle enzyme-linked immunosorbent assay (VLP-ELISA), which was used in the 2vHPV trials in addition to the PBNA. The competitive Luminex immunoassay (cLIA), which was developed by Merck®, detects antibodies directed against only one neutralizing epitope, whereas the VLP-based assays, either ELISA or in a multiplexed manner, will detect all HPV-specific antibodies. The fluorescent multiplex-based assay can rapidly detect antibodies against multiple HPV serotypes simultaneously and is a good alternative to ELISA. Lastly, the *in-situ* purified glutathione S-transferase L1-based Multiplex immunoassay (GST-L1-MIA), measuring antibodies against conformational and linear epitopes, has proven to be a useful assay in population studies. All these serological assays have different characteristics, but all can be used for the determination of HPV-specific vaccine derived antibodies. For the detection of natural or vaccine-induced antibodies, the cLIA and VLP-MIA are considered suitable alternatives to the PBNA [66].

1.1.3.6.3 Serosurveillance of HPV-antibodies in the Dutch population

To obtain insight into age-specific seroprevalence for diseases that are included in the Dutch National Immunization Programme (NIP), every decade a nationwide seroprevalence study (PIENTER) is conducted. To provide the Health Council with seroprevalence data that could be used to provide advice on the age of the catch-up campaign of HPV vaccination [1], a subset of girls and young women was selected from the second PIENTER study (2006/2007) and analysed. Seroprevalence for HPV6/11/16/18 among girls aged 11-26 years was assessed with the cLIA, measuring neutralizing antibodies. All girls below the age of 17 were negative for HPV16/18. From the age of 17 years onwards, the seroprevalence steeply increased, following the increasing percentage of women starting to be sexually active. The highest seroprevalence were seen for HPV6 and HPV16 [67].

In a later stage, the complete nationwide serumbank was analysed, albeit with a different assay (VLP-MIA), and age-related seroprevalence of seven hrHPV serotypes (HPV types 16, 18, 31, 33, 45, 52 and 58) was determined in cohorts born before the introduction of the HPV vaccine. Seroprevalence was assessed using a validated VLP-multiplex immunoassay, measuring all IgG secreted antibodies. An increase in seroprevalence was seen after sexual debut (15-19 years-old) in both males and females, which was most clearly in females and for type HPV16 (Figure 1.1.5) [68].

As there are also HPV serology results available from the first PIENTER study (1995-1996), comparison of seroprevalence profiles is possible. The overall seroprevalence increased between both PIENTER study periods. In age cohorts of people older than 15 years, a significant increase of 3.1% regarding HPV type 16, 18, 31 and 45 was seen in the second study compared with the first study. Moreover, the combination of HPV16/18 showed a clear increase during this 10-year time interval, as well as a shift of the peak of HPV16 seroprevalence to a younger age group (from 25-29 to 20-24 years of age). Factors that possibly contributed to the increase in HPV seroprevalence might be changes in sexual behaviour, e.g. a younger age of sexual debut and/or more sexual partners, an increased risk of an STI and an increase in the higher population mobility, such as immigration of populations that are at higher risk for HPV seropositivity [69]. At present, the third round of the PIENTER study (PIENTER3) is ongoing (2016-2017 data-collection). This will provide the opportunity to study changes in antibody levels and risk factors in the general population in a time period after the introduction of the HPV vaccine.

Vink et al. used a two-component mixture model to estimate HPV16 seroprevalence using data from the PIENTER2 study (2006/2007). She found different seroprevalence profiles, depending on sex and age. In the mixture model analysis, seroprevalence was found to increase from adolescence onwards (coinciding with the estimated time of sexual debut) in men and women. Among men, the seroprevalence was relatively stable from 40 years onwards, while in women there was a decreasing trend from 50 years onwards [70].

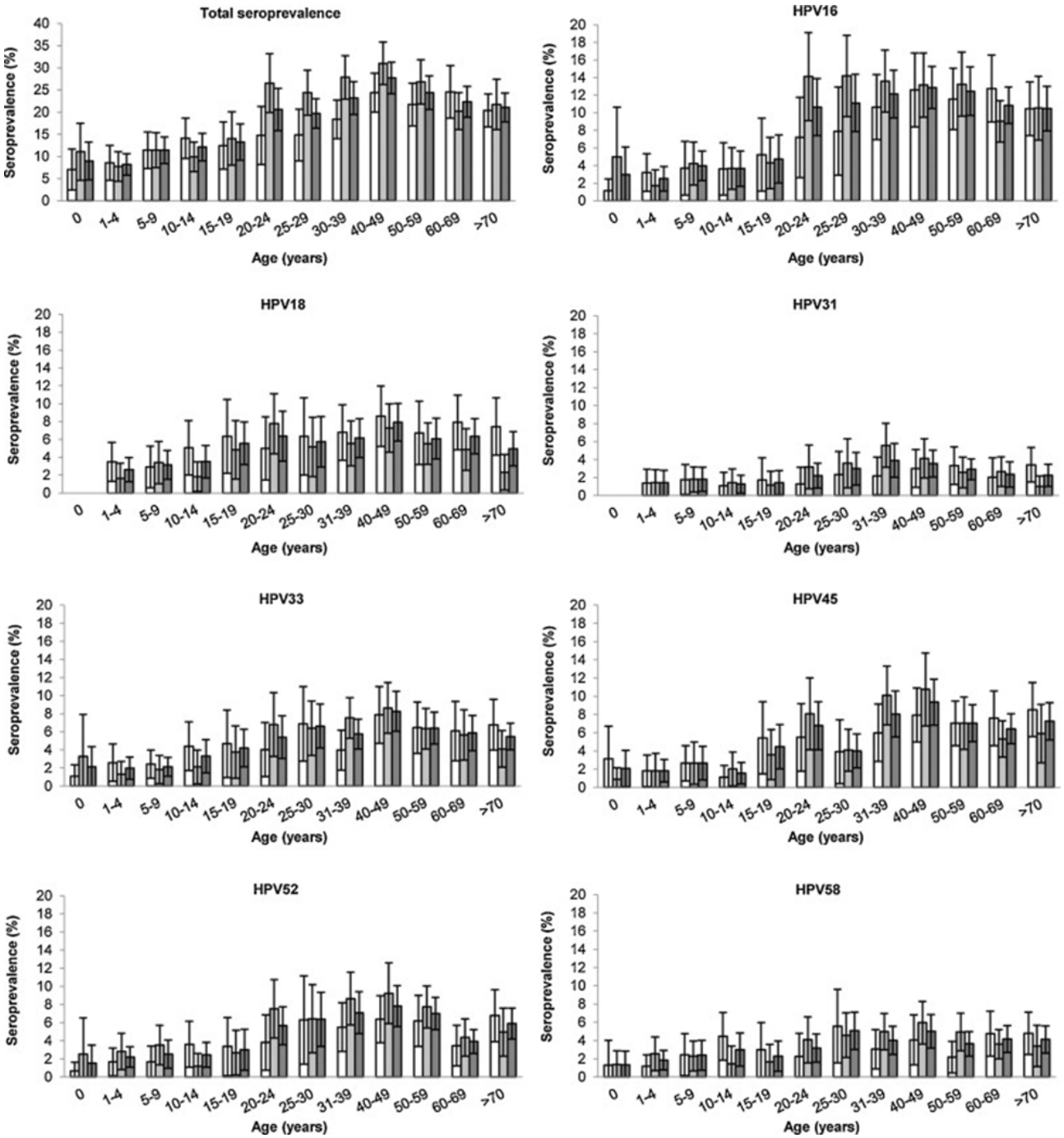

Figure 1.1.5 HPV seroprevalence of seven high-risk types in the Dutch population among males (white bars), females (light grey bars) and overall (dark grey bars)
Error bars indicate the 95% confidence interval.
From Scherpenisse et al., 2012 [68].

With the introduction of the bivalent HPV vaccine in the Dutch NIP in 2009, the HAVANA (HPV Among Vaccinated and Non-vaccinated Adolescents) study was initiated, which is still ongoing. The primary aim of this study is to assess the vaccine-effectiveness against HPV16/18 persistent infections (see Section 2.3.4.2). This study also showed that the bivalent HPV16/18 vaccine induces high serum antibody concentrations. Up to six years post-vaccination, seroprevalence among completely vaccinated participants (three-dose regimen) in the HAVANA-study remained 100% for HPV16 and HPV18. High concentrations of antibodies against HPV16 and HPV18 also persist up to six years post-vaccination (Figure 1.1.6). In addition, antibodies are present in the cervical secretion (CVS) and the levels correlate well with the serum antibody levels. Although HPV-specific antibody levels in CVS were lower compared with serum, they remained fairly constant over two years post-vaccination and therefore might contribute to the protective environment of the cervix [71].

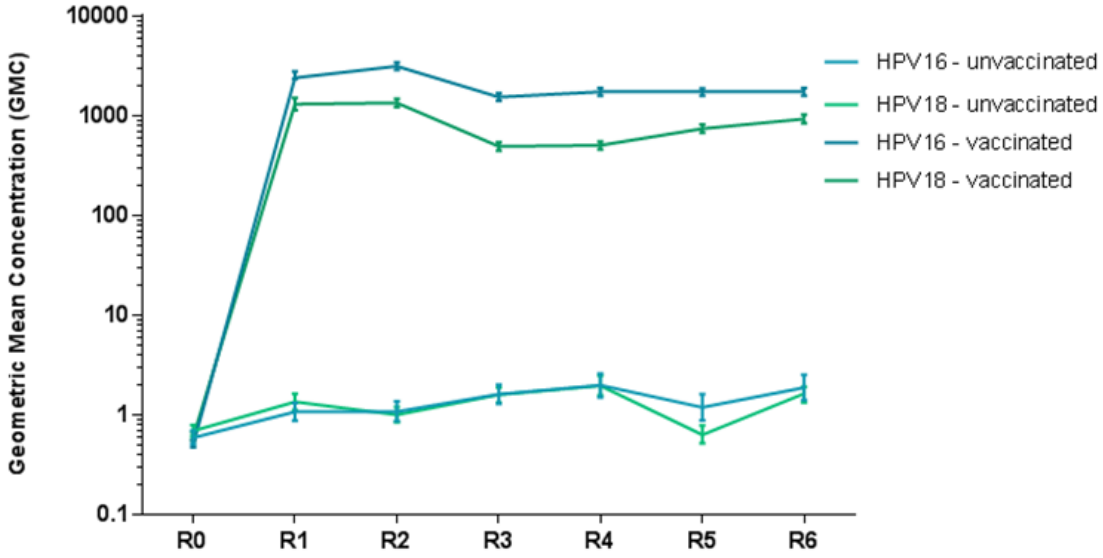

Figure 1.1.6 Geometric Mean Concentrations (GMC, IU/ml) of HPV types 16/18 in vaccinated and unvaccinated girls in the HAVANA-study up to six years post-vaccination
Data for R0 was sampled before vaccination.

The seroprevalence of HPV types is much higher in high-risk groups such as MSM, sex workers or HIV+ individuals. For instance, the seroprevalence measured in the H2M-study of HPV16 in HIV- and HIV+ MSM was 37.1% and 62.7%, respectively. The seroprevalence for HPV18 was 29.1% in the HIV-negative MSM group and 42.5% in the HIV+ MSM group. Similar patterns were observed for HPV type 31, 33, 45, 52 and 58, which indicates that the seroprevalences of hrHPV types are high among unvaccinated MSM [72]. In a study amongst Dutch STI clinic visitors (PASSYON) HPV seropositivity in MSM was 34% and in men who have sex with women 19%.

1.2 HPV-related disease

1.2.1 Cervical cancer

Invasive cervical cancer or a precursor lesion is almost always caused by a persistent hrHPV infection [73, 74]. The first microscopic evidence of precancer can be found within a few years after infection [74, 75]. The median duration from onset of CIN2/3 to invasive cervical cancer is estimated by Vink et al. to be 23.5 years (95% CI 20.8-26.6) [16]. Different classifications of HPV-related abnormalities are shown in Figure 1.2.1 [74].

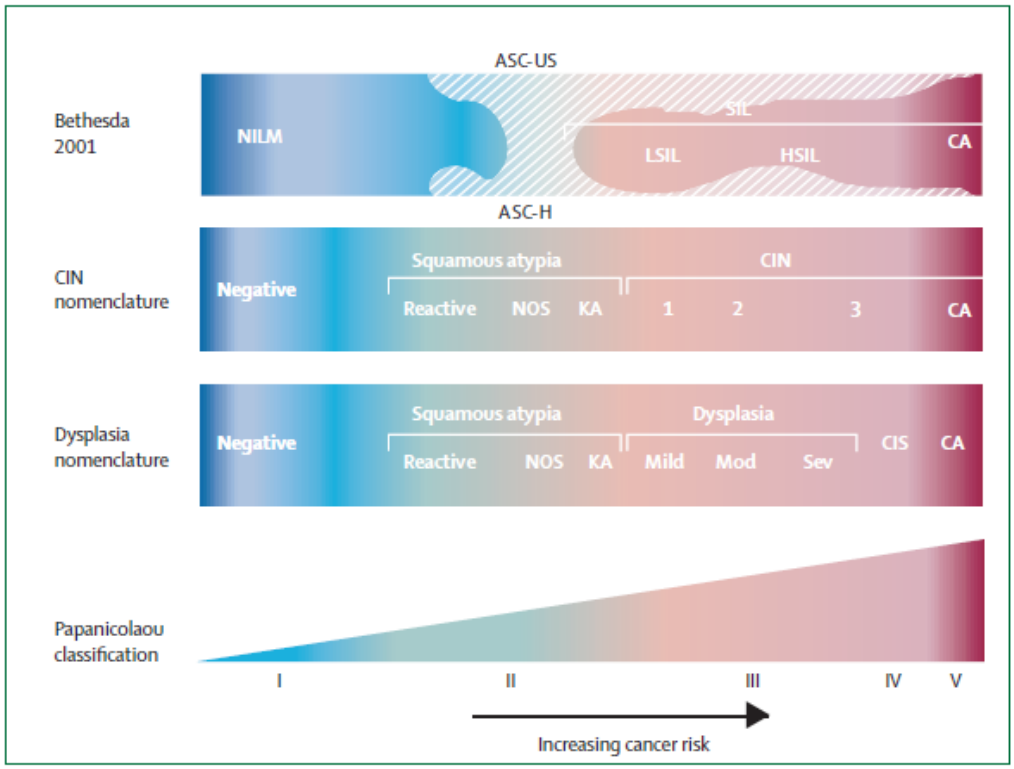

Figure 1.2.1 Comparative classification of HPV-related microscopic abnormalities
From Schiffman 2007 [74].
CIN = cervical intraepithelial neoplasia; ASC-US = atypical squamous cells of undetermined significance; ASC-H = atypical squamous cells, cannot exclude an HSIL; NILM = negative for intraepithelial lesion and malignancy; ASC = atypical squamous cells; SIL = squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion; HSIL = high-grade squamous intraepithelial lesion; KA = koilocytotic atypia; HPV = human papillomavirus; CA = invasive carcinoma; NOS = not otherwise specified; Mild = mild dysplasia; Mod = moderate dysplasia; Sev = severe dysplasia; and CIS = carcinoma in situ.
Equivocal interpretations of ASC-US and ASC-H are noted with stippling, the amount and colour of which suggests the expected frequencies within the differential diagnosis.

The chance that CIN1 will regress is high, therefore no treatment is recommended. For CIN2, treatment should be individually considered, depending on the chance of progression and complications from the treatment on fertility. Treatment for CIN3 is necessary because of the chance of it progressing to cancer. CIN can be treated by an excision procedure, by destruction of the transformation zone or through medication [76].
Around 80% of the patients with cervical cancer are diagnosed at an early stage, mostly by cervical cancer screening, in which the cancer is

restricted to the cervix. In less than one-fifth of the patients, the cancer has progressed outside the cervix to lymph nodes or to other organs. Treatment of cervical cancer consists of surgical removal of the uterus and, depending on the progression of the cancer, additional radiotherapy and/or chemotherapy. The 5-year survival rate of patients with cervical cancer is currently around 67%, but ranges from 15 to 90%, depending on the stage [77].

The HPV prevalence increases with pathology from 12% in case of normal cytology to 92% for cervical cancers [78, 79], although this varies by HPV type [80]. In Table 1.2.1, the hrHPV type distribution in women with cervical lesions/cancer is presented [79, 81]. HPV16 is most common in women with high-grade cervical lesions (HG-CIN) or cervical cancer.

Table 1.2.1 Estimates of hrHPV type prevalence among women with cervical lesions/cancer in Europe

hrHPV-type	*Tjalma 2013*		*Serrano 2015*
	HG-CIN % (95% CI)	ICC % (95% CI)	Cervical cancer
16	59.9 (51.5–68.1)	63.3 (58.8–67.7)	65.5 (63.4-67.6)
18	3.6 (1.4–6.9)	15.2 (8.6–23.3)	7.3 (6.2-8.5)
31	9.0 (6.0–12.6)	3.7 (1.2–7.5)	3.4 (2.6-4.2)
33	10.5 (9.4–11.6)	4.6 (2.0–8.2)	5.7 (4.7-6.8)
35	2.5 (0.9–4.8)	1.1 (0.4–2.1)	
39	0.4 (0.0–7.0)	1.1 (0.0–6.2)	
45	1.9 (0.1–5.9)	5.3 (2.9–8.3)	3.9 (3.1-4.8)
51	2.0 (0.1–6.3)	0.4 (0.0–3.9)	
52	3.9 (0.7–9.5)	1.7 (0.0–6.8)	1.9 (1.4-2.6)
56	0.9 (0.0–5.8)	0.8 (0.0–6.0)	
58	3.2 (1.6–5.4)	1.1 (0.0–3.6)	1.3 (0.9-1.9)
59	0.4 (0.0–7.4)	0.6 (0.0–5.8)	
66	0.4 (0.0–4.6)	0.2 (0.0–9.5)	
68	0.8 (0.0–2.7)	1.3 (0.0–6.3)	

CI = confidence interval; ICC = invasive cervical cancer; HG-CIN = high-grade cervical intraepithelial lesions; hr = high-risk.

1.2.1.1 Epidemiology of cervical cancer in the Netherlands

Annually in the Netherlands, about 700 women are diagnosed with cervical cancer. About 200 women die as a result of cervical cancer [77, 82]. Figure 1.2.2 shows the age-specific incidence of cervical cancer and deaths due to cervical cancer in the Netherlands. The number of cervical cancer cases has slightly increased since 2000, but the number of deaths related to cervical cancer have remained more or less stable [83, 84].

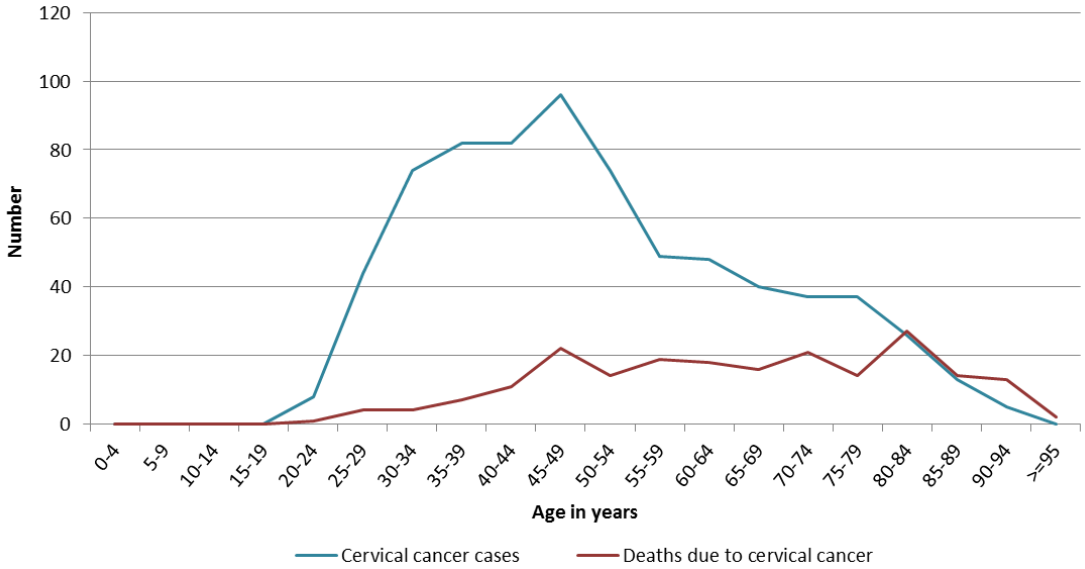

*Figure 1.2.2 Age-specific number of cervical cancer cases and deaths due to cervical cancer in the Netherlands in 2015**

*preliminary data

The incidence of CIN1 in Dutch females 30 to 64 years of age increased between 2009 and 2012. Also, an increase was seen in incidence of CIN2 and CIN3 in 2009 up to 2012. However, the number of incidences in 2013 stabilized (Figure 1.2.3) [83].

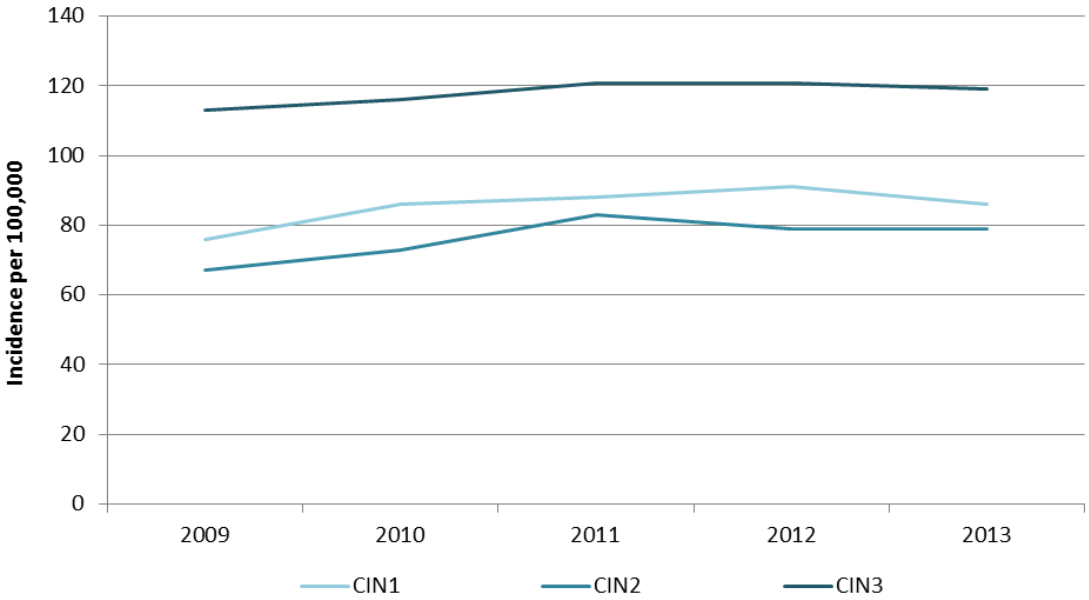

Figure 1.2.3 Incidences of CIN in women aged 30-64 years in the Netherlands in 2009-2013, per 100,000 women

CIN = cervical intraepithelial lesions

1.2.1.2 Screening programme cervical cancer

Up to 2017, all females between 30 and 60 years of age were invited to the screening programme for cervical cancer every five years. Annually,

almost 800,000 women received an invitation to have a smear collected at their general practitioner's office for cytological examination. Each year, participation is stable at around 65%. The degree of protection, i.e. the 5-year reach of women at risk, is 69-80%, depending on age. The percentage of mild abnormal smears increased from 2010 to 2013, but stabilized in 2014 (Table 1.2.2). Among women with an abnormal smear who were advised to see a gynaecologist, more than 90% followed the follow-up or referral advice [83].

Table 1.2.2 Recommendations in the cervical screening programme based on cytological result per year (LEBA 2015 [83])

	2010	2011	2012	2013	2014
No follow-up	94.3%	94.0%	93.9%	93.7%	93.8%
Follow-up at 6 months	3.2%	3.4%	3.5%	3.7%	3.7%
Referral to gynaecologist	0.8%	0.9%	0.8%	0.8%	0.9%
Repeat smear	1.6%	1.8%	1.8%	1.8%	1.7%

In 2017, a revised screening programme is starting with several changes. Women between 30 and 60 years of age will still be invited to have a cervical smear at their general practitioner's (GP) practice every five years, which will be tested for the presence of hrHPV (Table 1.2.3). Women who do not respond to the invitation can receive a self-sampling kit at home at their request. For women between 40 and 50 years of age who tested negative for hrHPV, the interval for screening will be extended to 10 years. Only if a sample tests positive for hrHPV will a cytological examination be carried out. Depending on the result, the women will be offered a referral to the gynaecologist or will be invited for a follow-up cytological examination after 6 months (Figure 1.2.4) [85, 86].

Table 1.2.3 Differences between the cervical screening programme up to 2017 and the cervical screening programme from 2017 onwards [85]

	Cervical screening programme up to 2017	Cervical screening programme from 2017 onwards
Test	cytological examination	hrHPV test, potential followed by cytological examination
Target group	30 to 60 years	30 to 60 years
Number of screenings rounds	7	minimal 5, maximum 8
Age of invitations	30, 35, 40, 45, 50, 55, 60	30, 35, 40, 50, 60 45, 55 of 65 in case of testing hrHPV-positive 5 years before
Follow-up at 6 months	cytological examination (and hrHPV test)	cytological examination

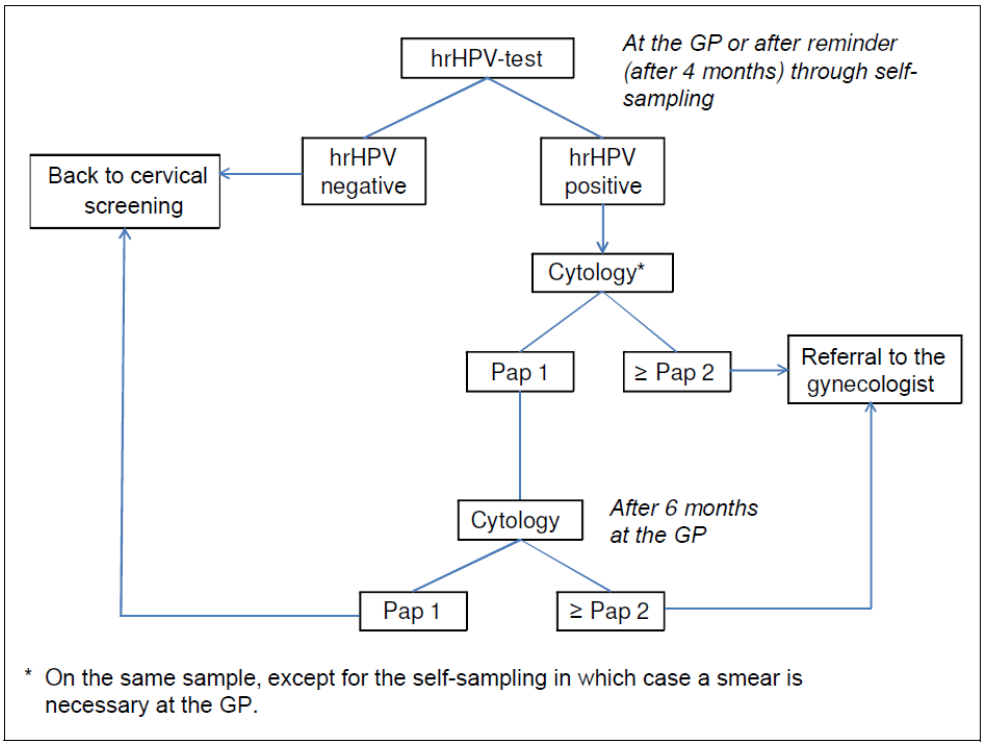

Figure 1.2.4 Flowchart of a screenings round in the revised cervical screening programme [85]
Hr = high-risk; GP = general practitioner; Pap = Papanicolaou test.

The revised screening programme is estimated to be 13-15% more effective than the previous screening programme run up to 2017 in terms of prevented cervical cancer cases and deaths. Furthermore, the total costs for screening will be reduced by about 35% and, including diagnostics and treatment, by about 20% [87]. In these current calculations, HPV vaccination is not taken into account.

HPV vaccination is expected to have an effect on the incidence of premalignant abnormalities, which affect the effectiveness of screening [85]. The first group of vaccinated girls reach the eligible age for cervical screening in 2023.
Steens et al. estimated that, by taking a mother's screening participation as a proxy for girls' future screening, only 13% of the girls will not participate in either programme, compared with 23% if screening alone is available [88].

1.2.2 Other HPV-related cancer

Besides cervical cancer, HPV also causes other cancers, such as vaginal, vulvar, penile, anal, oral cavity, pharyngeal and oropharyngeal cancers [89].

Cancer of the vagina, vulva, penis and anus are relatively rare. However, incidences of anal cancer are increasing [89]. Of all gynaecological cancers, 2% are primary tumours in the vagina, secondary vagina tumours were found more frequently. The five-year survival of vaginal carcinoma ranged between 44 and 92%, depending on the stage. Radiotherapy is the first choice of treatment, but for minor

lesions surgery can be used. Only 2-5% of the genital malignant tumours are localized at the vulva, in which surgery is the first choice of treatment. Treatment of penile carcinomas consists of laser therapy and partial amputation of the penis, possibly in combination with dissection of the inguinal lymph node, radiotherapy and/or chemotherapy. Treatment of invasive anal carcinomas consists of surgery, radiotherapy or systemic therapy. In the case of precursor lesions AIN2/3, patients should be treated, preferably with electro or infrared caogulation [76].

In Europe every year, an estimated 139,531 new cases of head and neck cancers occur and an estimated 63,470 people die due to these cancers [90]. The fraction of cancers of the oral cavity and pharynx associated with HPV varies between studies, depending on the accuracy of the distinction of cancer sites, the competing effect of tobacco and the quality of tissue biopsies and HPV testing. Cancers of the oral cavity and oropharynx are strongly associated with smoking and drinking [89]. However, patients with HPV-positive oropharyngeal cancer have a better clinical outcome than patients with HPV-negative oropharyngeal cancer and other head neck cancer (about 80% vs. 40%) [91].
The prevalence of any HPV type in these cancers is presented in Table 1.2.4 [81, 90-96]. The HPV type distribution for types included in the bivalent, quadrivalent and/or nonavalent vaccine is shown per cancer type in Table 1.2.5 [81, 90-96].

Table 1.2.4 Overall HPV prevalence in HPV-associated cancers in men and women

Reference	Cancer type	Study population	Study period	Region	N	Overall HPV prevalence (95% CI)
Alemany 2016 [90]	Penile	Men	1983-2011	Europe	419	32.2% (27.8-36.9%)
Serrano 2015 [81]	Vaginal	Women	1986–2011	Worldwide	408	74.3%
	Vulvar		1980–2011		1,709	28.6%
	Anal		1990–2010		329	90.0%
Alemany 2015 [91]	Anal	Men and women	1986-2011	Europe	169	87.6 %
Alemany 2014 [92]	Vaginal	Women	1986-2011	Europe	152	71% (63-78%)
de Sanjose 2013 [94]	Vulvar	Women	1980-2011	Europe	903	18.3%
De Vuyst 2009 [95]	Vaginal	Review of articles published between January 1986 and March 2008		Europe	8 studies	76.8%
	Vulvar				34 studies	34.7%
	Anal				13 studies	84.2%
Castellsagué 2016 [93]	Oral	Men and women	From 1990 onwards	Worldwide	1,264	7.4%
	Nasopharyngeal				101	7.9%
	Oropharyngeal				1,090	24.9%
	Hypopharyngeal				127	3.9%
	Pharyngeal unspecified				56	21.4%
	Laryngeal				1,042	5.7%
Ndiaye 2014 [96]	Oral	Review of articles published between February 1, 2004 and February 29, 2012		Europe	1,963 (39 studies)	17% (10-26%)
	Oropharyngeal				1,891 (30 studies)	41% (33-50%)
	Laryngeal / Hypopharyngeal				1,484 (32 studies)	21% (14-29%)

CI = confidence interval.

Table 1.2.5 HPV type distribution for types included in the bivalent, quadrivalent and/or nonavalent vaccine in HPV-associated cancers in men and women

Ref.	Anatomic site	HPV 6 (95% CI)	HPV 11 (95% CI)	HPV 16 (95% CI)	HPV 18 (95% CI)	HPV 31 (95% CI)	HPV 33 (95% CI)	HPV 45 (95% CI)	HPV 52 (95% CI)	HPV 58 (95% CI)
Alemany 2016 [90] (worldwide)	Penile	3.7%	1.5%	68.7%	1.5%	0.8%	2.9%	2.7%	1.5%	1.3%
Serrano 2015 [81] (Europe)	Vaginal	0.9% (0.0-5.1%)	0.9% (0.0-5.1%)	66.6% (56.9-75.4%)	4.6% (1.5-10.5%)	2.8% (0.6-7.9%)	3.8% (1.0-9.2%)	2.2% (0.2-6.5%)	1.9% (0.2-6.5%)	3.7% (1.0-9.2%)
	Vulvar	0.0% (0.0-2.1%)	0.6% (0.0-3.2%)	71.8% (64.5-78.4%)	1.8% (0.4-5.0%)	2.5% (0.6-5.8%)	5.5% (2.8-10.3%)	1.1% (0.1-4.1%)	0.6% (0.0-3.2%)	0.8% (0.0-3.2%)
	Anal (women)	1.0% (0.0-5.6%)	1.0% (0.0-5.6%)	87.6% (79.4-93.4%)	3.1% (0.6-8.8%)	1.0% (0.0-5.6%)	2.1% (0.3-7.3%)	0.0% (0.0-3.7%)	0.0% (0.0-3.7%)	0.0% (0.0-3.7%)
Alemany 2015 [91] (Worldwide)	Anal	1.8%	1.1%	80.7%	3.6%	1.9%	2.7%	0.9%	0.7%	1.8%
Alemany 2014 [92] (Europe)	Vaginal	0.9%	0.9%	66.6%	4.6%	2.8%	3.8%	2.2%	1.9%	3.7%
De Sanjose 2013 [94] (worldwide)	Vulvar	0.7%	0.2%	72.5%	4.6%	1.0%	6.5%	3.3%	1.9%	1.0%
De Vuyst 2009 [95] (worldwide)	Vaginal	*	*	53.7%	7.6%	5.6%	*	*	*	*
	Vulvar	*	*	32.2%	4.4%	*	4.5%	*	*	*
	Anal	*	*	73.4%	5.2%	*	4.8%	*	*	*
Castellsagué 2016 [93] (worldwide)	Oral	0.0%	1.1%	68.8%	1.1%	0.0%	0.0%	0.0%	4.3%	1.1%
	Nasopharyngeal	0.0%	0.0%	75.0%	0.0%	0.0%	0.0%	0.0%	12.5%	0.0%
	Oropharyngeal	0.4%	0.0%	83.0%	1.8%	0.0%	3.3%	0.4%	0.0%	0.7%
	Hypopharyngeal	0.0%	0.0%	80.0%	0.0%	0.0%	20.0%	0.0%	0.0%	0.0%
	Pharyngeal unspecified	0.0%	0.0%	66.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	Laryngeal	6.6%	1.7%	50.8%	5.1%	3.4%	3.4%	8.5%	0.0%	1.7%

Ref.	Anatomic site	HPV 6 (95% CI)	HPV 11 (95% CI)	HPV 16 (95% CI)	HPV 18 (95% CI)	HPV 31 (95% CI)	HPV 33 (95% CI)	HPV 45 (95% CI)	HPV 52 (95% CI)	HPV 58 (95% CI)
Ndiaye 2014 [96] (worldwide^)	Oral	0.8% (0.1-1.9%)	0.5% (0.0-1.2%)	14.9% (11.1-19.1%)	5.9% (3.4-9.0%)	0.1% (0.0-0.5%)	0.1% (0.0-0.4%)	0.0% (0.0-0.0%)	0.0% (0.0-0.0%)	0.0% (0.0-0.0%)
	Oropharyngeal	0.0% (0.0-0.0%)	0.0% (0.0-0.0%)	40.6% (34.4-47.0%)	0.2% (0.0-0.5%)	0.0% (0.0-0.0%)	0.7% (0.3-1.1%)	0.0% (0.0-0.0%)	0.0% (0.0-0.0%)	0.0% (0.0-0.1%)
	Laryngeal / Hypopharyngeal	1.4% (0.3-3.0%)	0.3% (0.0-0.8%)	13.4% (9.1-18.4%)	1.6% (0.6-3.1%)	0.0% (0.0-0.1%)	0.3% (0.0-0.7%)	0.0% (0.0-0.3%)	0.0% (0.0-0.3%)	0.0% (0.0-0.2%)

*See figure in original article
^ For Europe see figure in original article
CI = confidence interval.

The HPV prevalence was higher in cases with intraepithelial neoplasia than in cancer cases, i.e. 89-100% and 74-88% in anal intraepithelial neoplasia and anal cancer, respectively [81, 91, 95], 80-87% and 28-35% in vulvar intraepithelial neoplasia and vulvar carcinoma, respectively [81, 95], 95-98% and 71-77% in vaginal intraepithelial neoplasia and vaginal carcinoma, respectively [81, 92, 95] and 89% and 32% in penile high grade squamous intraepithelial lesions and penile cancer, respectively [90].
HPV prevalence also differed by histological diagnosis (30-94% for invasive vaginal cancer, 27.3-95.9% for invasive anal cancer, 14.7-75.3% for invasive penile cancer) [90-92, 95].
The HPV prevalence was significantly higher in cases involving a younger age at diagnosis (OR women <60 years vs. >71 years: 3.63, 95% CI 2.40-5.47) [95]. HIV+ individuals had a higher HPV prevalence in AIN2/3 (96.7%) than HIV- individuals (90.1%) [95]. For head and neck cancers, no significant differences in HPV prevalence were found between men and women [96].
Multiple HPV infections were more common in precancerous lesions than in cancers, indicating that in general only one type progress towards cancer [81, 90, 91, 94, 95].

1.2.2.1 Epidemiology of HPV non cervical cancer in the Netherlands

Annually, about 50 women are diagnosed with vaginal cancer, 300-400 women with vulvar cancer, about 140 men with penile cancer and about 200 people (about 110 women and 90 men) with anal cancer. About 25, 95-140, 35, 40 people die due to vaginal, vulvar, penile and anal cancers per year, respectively. Cancer of the mouth and pharynx is diagnosed in 800-900 people every year and approximately 270 and 300 die due to these cancers, respectively [77, 82]. Figures 1.2.5 and 1.2.6 show the age-specific and gender-specific incidence of HPV-associated cancers and deaths due to HPV-associated cancers other than cervical cancer in the Netherlands. The incidence of HPV-associated cancers and deaths related to HPV-associated cancers has remained more or less stable in past years [84].

Figure 1.2.5 Age-specific and gender-specific number of HPV-associated cancers other than cervical cancer in the Netherlands in 2015 (NKR [77])*
*preliminary data

Figure 1.2.6 Age-specific and gender-specific number of deaths due to HPV-associated cancers other than cervical cancer in the Netherlands in 2015 (CBS [82])*
*preliminary data

In the last two decades, the HPV prevalence in oropharyngeal squamous cell carcinomas (OPSCC) in patients treated at the VUmc significantly increased from 5.1% in 1990 to 29.0% in 2010 [97]. In a cohort of Dutch patients with OPSCC, an increase in HPV prevalence was found between 1980 and 1989 (28%) and between 1990 and 1999 (38%), but not for the last decade 2000-2009 (38%) [98].

1.2.3 Other HPV-related diseases

1.2.3.1 Genital warts

Other than cancer, HPV can also cause anogenital warts (AGW). It is difficult to obtain reliable incidence figures on AGW worldwide. Surveillance data on the pre-vaccine area from developed countries

indicated an annual incidence of 0.1% to 0.2%, with a peak occurring at teenage and young adult ages [78].

According to the literature, approximately 90% of genital warts are caused by HPV types 6 and 11, although often many different HPV types are present at the genital site [99-101]. The median time from HPV6/11 infection to the development of AGW varies in the literature between two and 10 months, but can be up to 18 months. About 60-80% of the sexual partners of patients with AGW are also infected with HPV [101-103].

Usually, AGW caused by HPV6/11 are characterized by flesh or grey-coloured, outward growing swellings with sharp edges and with a cauliflower-like surface. AGW most often occur in clusters of about 5-15 lesions, but can also occur singly. Possible symptoms include pain, burning, discomfort, itching and vaginal discharge or discharge from the urethra [103]. Moreover, AGW can have an impact on the emotional well-being of patients. This impact is generally greater for women than for men and, among women, sexual and clinical factors can influence the impact of AGW on the well-being [104]. In men, AGW are most often found on the penile shaft, scrotum, urethral meatus and the perianal area. In women, AGW are most often found on the vaginal opening, vulva, clitoris, perineum and perianal area. They can also occur on internal surfaces, such as inside the vagina and on the cervix. Immune-incompetent patients (and some pregnant women) especially can develop many and very large warts. In rare cases, patients with AGW can develop a Buschke-Loewenstein tumour or giant condyloma [103].

Treatment is focused on the removal of visible warts and not on treatment of the HPV infection. The cure rate with the available treatment is 32-88%, but the recurrence rate is high. Home therapy includes imiquimod cream, podofilox solution or gel, and sinecatechins ointment. Clinical therapy includes cryotherapy, electrocautery, laser, bichloracetic acid, trichloracetic acid and surgical removal. In absence of treatment, the regression of warts occurs in 90% of the patients within two years after diagnosis [102, 103].

1.2.3.1.1 Epidemiology in the Netherlands

Surveillance of genital warts in the Netherlands is based on data from STI clinics and GPs. AGW are usually diagnosed based on clinical appearance. Not all people attending the STI-clinic are tested for AGW; only people who report symptoms undergo physical examination. The proportion of STI-clinic attendants that were diagnosed with AGW declined from 2.9% in 2009 to 1.4% in 2014. In 2015, 1.5% of all STI-clinic attendants were diagnosed with AGW, corresponding to 2,000 diagnoses. At the GP, the estimated number of AGW episodes was 37,826 in 2014. This number is based on data from GPs participating in the NIVEL primary care database and extrapolated to the whole of the Netherlands. The reporting rate at the GP increased from 1.7 per 1,000 persons in 2009 to 2.3 per 1,000 persons in 2014. At the STI-clinic and the GP, the proportion diagnosed with AGW was higher among men than among women [105].

1.2.3.2 Recurrent respiratory papillomatosis (RRP)

RRP is a rare syndrome of recurring proliferations of multiple papillomas in the respiratory tract. Most commonly, RRP is caused by HPV11, followed by HPV6 [106]. In the United States, juvenile-onset RRP was estimated on the basis of private and public insurance claims. The overall adjusted incidence in 2006 was 0.51 and 1.05 per 100,000 population, respectively [107]. Mostly affected are young children or young adults. For young children, transmission from mother to child during delivery or in utero was found. For young adults, oral sex might lead to RRP. Not all exposure to HPV in the respiratory tract leads to RRP; immunodeficiency and related infections are thought to be risk factors. RRP cannot be cured, but spontaneous regression is possible. Treatment is focused on reducing the complaints of patients. This is most often done through surgery. The prognosis of RRP is usually good and morbidity is low [106].

1.2.3.2.1 Epidemiology in the Netherlands

Information on the epidemiology of RRP in the Netherlands is scarce. It has been estimated that the prevalence of laryngeal papillomatosis is 4-7 per 100,000 population. This means there are approximately 900 patients in total in the Netherlands [108].

1.3 Overall HPV Disease burden

Globally, HPV infection prevalence in women with normal cervical cytology is estimated at 11-12%, and HPV played a causal role in an estimated 610,000 cancer cases in 2008 [78]. Although much research has been conducted on characterizing the burden of HPV-related disease, both globally [109, 110] and at a national level [111], the outcomes typically reported are mortality rates and annual cancer incidence. To gain a better understanding of health burden attributable to HPV infection among the total population and to enable straightforward comparisons to be made between HPV and other infectious agents, or between men and women (because they experience different conditions), measuring disease burden using a composite or summary metric is desirable. The disability-adjusted life-year (DALY) combines the impact of a disease on both mortality and morbidity [112, 113], and is therefore suitable for comparing populations and investigating temporal trends.

To address the goal of estimating the past and present total population-level disease burden due to HPV in the Netherlands, a recent study applied DALY methodology to national-level data [114]. The DALY was used to quantify the impact of all health outcomes with evidence for a causal role of HPV infection. Registered cancer cases at all known or suspected sites associated with HPV infection in males and females were the primary data source. In addition, the burden of precancerous lesions (CIN-2/3) detected through cervical screening and the burden of AGW was incorporated into the computation. Separate DALY estimates were made for males and females, for different age groups and for different HPV types. This stratification is motivated by the relevance for public health decision-making, considering the sex and age specificity of HPV vaccination programmes and the composition of the available HPV vaccines. The past and future temporal trends in HPV-related disease

burden were also estimated. Forecasts were restricted to the period prior to the time at which the clinical impact of the current vaccination programme is expected to be observable (i.e. running up to 2023).

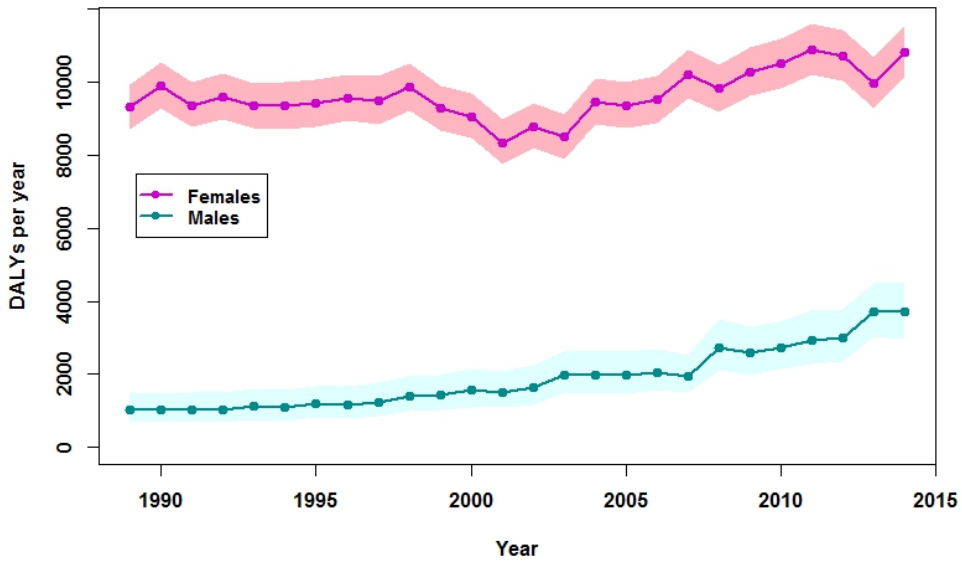

Figure 1.3.1 Estimated HPV-attributable disease burden (in DALYs) in the Netherlands over the period 1989-2014, aggregating over age and outcome. Shaded areas indicate 95% uncertainty intervals.
DALY = disability-adjusted life-year.

The annual total HPV-associated disease burden in the Netherlands was estimated for the 26-year study period 1989-2014. Annual cancer registrations for all sites with a well-established aetiological link to HPV infection (cervix, vagina, vulva, anus, oropharynx, penis) and for sites with a possible link to HPV infection (oral cavity, larynx) were retrieved from the Netherlands Cancer Registry (NKR). The estimation was conducted on the basis of data on the occurrence of the disease outcome (i.e. cancer, AGW, CIN-2/3), irrespective of aetiology, and the proportion of incident cases attributable to HPV infection was estimated using population-attributable fractions (PAFs). For cancer cases, disability associated with health states subsequent to diagnosis (associated with management, treatment and the consequences of treatment failure) was also included and case-fatality rates were applied to estimate the associated mortality.

This study found that an average annual disease burden of 1,889 DALYs (95% credible interval (CrI): 1,763-2,020) and 9,648 (95% CrI: 9,519-9,781) could be attributed to HPV infection in males and females, respectively, during the period 1989-2014. An overall rising trend was observed for both sexes (Figure 1.3.1), but this trend was steeper for males (103 DALYs/year) compared with females (46 DALYs/year). The temporal trend in females was 60 DALYs/year when excluding cervical cancer from the burden. Focusing on the recent study period (2011-2014) only, HPV infection was associated with an average disease burden of 3,346 DALYs/year (95% CrI: 2,973-3,762) and 10,600 (95% CrI: 10,260-10,960) in males and females, respectively. The share of the total disease burden borne by males increased from 9.8% in 1989 to

26% in 2014. The majority of the total disease burden was due to cervical cancer, although its share in the burden amongst women decreased from 89% in 1989 to 77% in 2011-2014, which is consistent with an effective screening programme. The largest burden in males was due to oropharynx site cancer: 51% of the total male HPV-related disease burden in 2011-2014. Anal cancers were responsible for the second largest burden in both sexes, with annual averages in 2011-2014 of 504 (15% of total) and 542 (5.1% of total) DALYs/year for males and females, respectively (Figure 1.3.2).

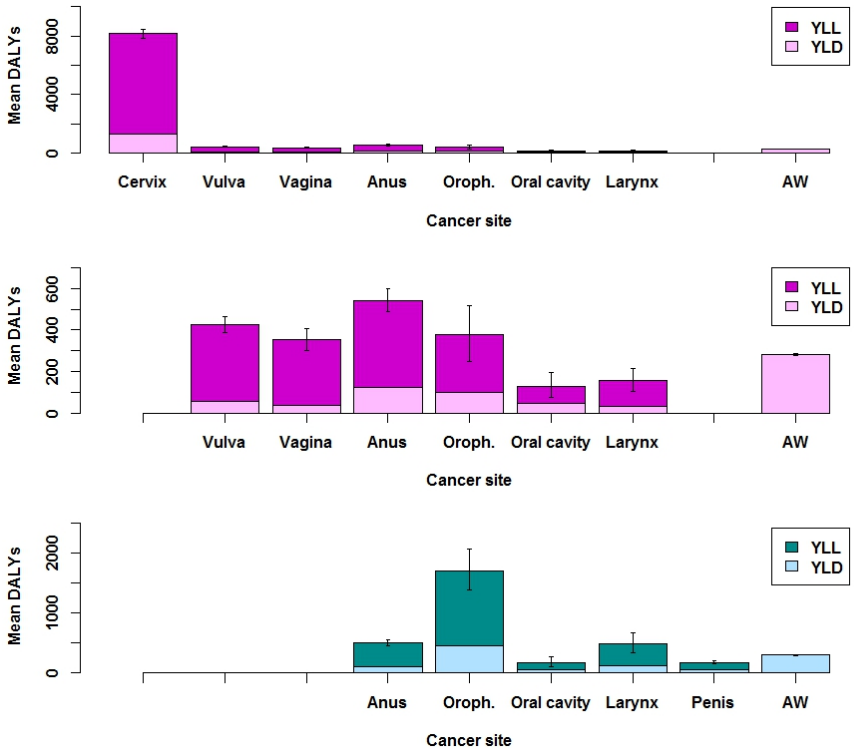

Figure 1.3.2 Average annual HPV-attributable disease burden (over the period 2011-2014) by outcome (including cancer sites and anogenital warts), plotted for females (top panel), females excluding cervical cancer (centre), and males (bottom).
DALY = disability-adjusted life-year; YLD = years lived with disability; YLL = years of life lost.

Age-group distributions of disease burden in the Netherlands varied between males and females. Cervical cancer was primarily responsible for a high disease burden in 30 to 49-year-olds, with peak DALYs/year in the 35-39 age-group. If cervical cancer was excluded, then the distribution of DALYs over age group for females closely resembled that for males. When excluding cervical cancer, a small percentage of the total disease burden occurred in persons under 40 years of age (3.5% and 8.1% for males and females, respectively). AGW accounted for an annual average of 296 DALYs/year (8.8% of the aggregated burden, period 2011-2014) for males and 280 DALYs/year (2.6% of the aggregated burden, 2011-2014) for females. Considering the most recent period (2011-2014) only, 79% of the female HPV-related disease burden was due to the bivalent high-risk types 16/18, a further 15% was due to the nonavalent-specific high-risk types 31/33/45/52/58, and 4.3% was attributed to the low-risk types 6/11. For the same period, 83% of the total burden in males was attributed to types 16/18, followed by 6.4% for the nonavalent-specific types and 2.8% for types 6/11.

The results of this study revealed a larger HPV-related disease burden in females than in males, which is due to the high cervical cancer burden. The estimated burden of male HPV-related disease was about 1.5-fold higher than the female burden from non-cervical disease, mainly due to the high oropharyngeal cancer burden. The estimated burden of HPV-related diseases other than cervical disease has steadily increased during the period, especially in males. The male share of the total disease burden increased from about 10% in 1989 to over 25% in 2014, due to rising incidence trends for all male cancers except for larynx. Under the assumption that current cancer incidence trends will continue, the rapidly rising share of males in the total disease burden is projected to continue in the near future.

2 Effectiveness of vaccines and vaccination

An extensive overview of analysis population and used definitions in this chapter is given in Appendix A. It should be noted that for different studies, slight nuances might exist in the study populations, although called equally.

2.1 Availability of vaccines

Summary

Three vaccines are currently licensed for the prevention of HPV-related diseases in Europe: a bivalent vaccine (Cervarix®) that includes the high-risk HPV types 16 and 18, a quadrivalent vaccine (Gardasil®) that includes, in addition to the high-risk types HPV16 and -18, the low-risk HPV types 6 and 11, and a nonavalent vaccine (Gardasil 9®) that covers 7 high-risk types (HPV16/18/31/33/45/52/58), as well as the two low-risk types HPV6 and -11.
All vaccines are licensed for the prevention of (precursors of) cervical, anal, vulvar and vaginal cancer. Additionally, the quadrivalent and nonavalent vaccines are indicated for the prevention of genital warts. Currently, no vaccines are licensed for the prevention of (precursors of) penile or oropharyngeal cancer. For adolescents 9-13/14 years of age, a two-dose vaccination schedule is indicated, while for recipients 15 years old and older, three-doses are required.

At this moment, three vaccines are licensed for the European market, which aim to prevent HPV-related diseases; a bivalent vaccine (Cervarix®) that includes the high-risk HPV types 16 and 18, a quadrivalent vaccine (Gardasil®) that includes, in addition to the high-risk types HPV16 and -18, also the low-risk HPV types 6 and 11, and a nonavalent vaccine (Gardasil 9®) that covers 7 high-risk types (HPV16/18/31/33/45/52/58), as well as two low-risk types HPV 6 and 11. The vaccines are licensed for the prevention of (precursors of) cervical cancer, anal cancer, vulvar cancer and vaginal cancer. Additionally, the quadrivalent and nonvalent vaccines prevent genital warts. The vaccines are not licensed for the prevention of penile or oropharyngeal cancer. In addition to the HPV type distribution, these vaccines mainly differ in the adjuvant used, i.e. AS04 for the bivalent vaccine and AAHS for the two other vaccines. The licensed vaccines, their composition, schedules and indications for Europe are shown in Table 2.1.1 The outcomes of the trials for licensure of the vaccines are described in detail further on below.

Table 2.1.1 Licensed prophylactic HPV vaccines and their indications

Vaccine	Composition	Adjuvant	Registered for	Indications	Doses
Cervarix® (bivalent)	20 µg HPV16 L1 protein 20 µg HPV18 L1 protein	AS04	♀ ≥9 yr.	* Caused by certain oncogenic types: CIN/AIS/CxCa AIN/ACa VIN VaIN	9-14 yr. 2D 0, 5-13 mo. 15-26 yr. 3D 0,1,6 mo.
			♂ ≥9 yr.	* Caused by certain oncogenic types: AIN/ACa	9-14 yr. 2D 0, 5-13 mo. 15-26 yr. 3D 0,1,6 mo.
Gardasil® (quadrivalent)	20 µg HPV6 L1 protein 40 µg HPV11 L1 protein 40 µg HPV16 L1 protein 20 µg HPV18 L1 protein	AAHS	♀ 9-26 yr.	* Caused by certain oncogenic types: CINAIS/CxCa VINVuCa VaIN/VaCa AINAca * Caused by vaccine types: GW	9-13 yr. 2D 0,6 mo 14-26 yr. 3D 0,2,6 mo
			♂ 9-26 yr.	* Caused by certain oncogenic types: AIN/ACa * Caused by vaccine types: GW	9-13 yr. 2D 0,6 mo 14-26 yr. 3D 0,2,6 mo
Gardasil9® (nonavalent)	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 20 µg HPV33 L1 protein 20 µg HPV45 L1 protein 20 µg HPV52 L1 protein 20 µg HPV58 L1 protein	AAHS	♀ 9-26 yr.	* Caused by certain oncogenic types: CIN/AIS/CxCa VIN/VuCa VaIN/VaCa AIN/Aca * Caused by vaccine types: GW	9-14 yr 2D 0, 6-12 mo 15-26 yr 3D 0,2,6 mo
			♂ 9-26 yr.	* Caused by certain oncogenic types: AIN/ACa * Caused by vaccine types: GW	9-14 yr 2D 0, 6-12 mo 15-26 yr 3D 0,2,6 mo

A=anal, AAHS=amorphous aluminium hydroxyphosphate sulfate adjuvant, AIS=Adenocarcinoma in situ, AS04=adjuvant system 04 (aluminium hydroxyl and monophosphryl lipid A), C=Cervical, Ca=carcinoma, Cx= Cervix, D=doses, GW=Genital warts, IN=intraepithelial neoplasia, V=vulvar, Va=Vaginal

2.1.1 *Cervarix®*

Registration of the bivalent vaccine for cervical cancer and its precursors is mainly based on efficacy studies conducted among 19,788 women ranging in age from 15 to 25 years. Outcomes of the vaccine trials were focused on incident and persistent infections from HPV16/18 and CIN2+ related to HPV16/18. Due to cross-protection, efficacy was also shown against HPV31/33/45/51-related six-month persistent infections and the development of CIN2+ lesions related to HPV31/33/45/51. Among 5,777

women that were 26 years old and older, efficacy against six-month persistent infections related to HPV16/18 was studied. Registration of the bivalent vaccine for adolescents (girls 9-14 years) was based on immunobridging; for adolescents (aged 9-14), a three-dose licensure was based on showing non-inferior immunogenicity for HPV16/18 in comparison with antibody levels in women that were 15-25 years old. In this latter group, efficacy against CIN2+ was shown. A similar immunobridging principle was used to register the two-dose schedule and for the licensure of the bivalent vaccine among males 10-18 years old. These boys showed non-inferior immunoresponses at seven months after the first dose compared to females (15-25 years old), receiving a three-dose schedule of the bivalent HPV vaccine. Licensure of a vaccine against anal cancer and its precursors was based on immunobridging between the bivalent and a comparator, i.e. quadrivalent vaccine. Immunogenicity among 9-14 year olds up to 12 months in a two-dose schedule and 18 to 45-year-old females for up to 60 months in a three-dose schedule was non-inferior or was even higher for the bivalent vaccine than that shown for the comparator vaccine, i.e. the quadrivalent vaccine. Considering the consistently higher immune responses to the bivalent vaccine compared with the quadrivalent vaccine, the expected benefit of the bivalent vaccine against anal lesions and cancers in males and females was therefore considered acceptable for licensure [115].

2.1.2 Gardasil®

The registration of the quadrivalent HPV vaccine was mainly based on efficacy studies conducted among women 16 to 26 years of age. Among 20,541 women, efficacy against HPV6/11/16/18 persistent infections, genital warts, vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VaIN), cervical intraepithelial neoplasia (CIN), adenocarcinoma in situ (AIS) and cervical cancer was studied. Also possible cross-protective efficacy against other high-risk HPV types was examined and this was found for HPV31.
Among 3,817 women aged between 24 and 45 years, efficacy against HPV6/11/16/18 incident infections and HPV16/18 related persistent infections, genital warts, VIN, VaIN, CIN, AIS and CxCa were studied. Among 4,055 males between the ages of 16 and 26, efficacy was studied against HPV6/11/16/18-related external genital warts, penile/perineal/perianal intraepithelial neoplasia (PIN) grades 1, 2, 3 and persistent infections. Registration of the quadrivalent vaccine for adolescents (9-15 years old) was based on immunobridging. For adolescents receiving a three-dose schedule, it was accepted that, when the immunogenicity among adolescents was comparable (non-inferior) to that found among young adults 16-26 years old, among whom efficacy was shown, then the efficacy is inferred to be comparable. Later immunobridging was also used to show comparable immunogenicity of a two-dose schedule among 9 to 13-year-old girls, compared with women 16-26 years old that received a three-dose schedule. Based on the available data, the CHMP endorsed the introduction of a two-dose schedule (0,6 months) in individuals 9 up to and including 13 years of age [116].

2.1.3 Gardasil 9®

For HPV6/11/16/18-related persistent infections and related diseases, registration and indications for the nonavalent vaccine were also based on immunobridging. A comparison of immunogenicity for these types was made between 9 to 15-year-old females and 16 to 26-year-old females and males that received either the quadrivalent vaccine (for which efficacy was shown) or the nonavalent vaccine. Studies conducted among 14,024 women aged between 16 and 26 years evaluated the efficacy against persistent infections, CIN2+, VIN2+, VaIN2+ against HPV31/33/45/52/58. Based on immunobridging, efficacy against HPV31/33/45/52/58 was also inferred for girls and boys aged 9-15 years. Also, the licensure of a two-dose schedule was based on immunobridging. Comparable immunogenicity in children 9-14 years old to the immunogenicity in three-dose recipients supported the additional licensure of the two-dose schedule [117].

2.2 Disease endpoints, intermediate endpoints, surrogates

Summary

In the evaluation of protection, persistent HPV infection of six months or longer can be used as an appropriate endpoint for most situations. An exception is the evaluation of vulvar/vaginal protection, in which HPV16/18-positive high-grade intraepithelial neoplasia is recommended as an endpoint. For oropharyngeal cancers, the only feasible endpoint is persistent HPV16/18 infection because of the lack of detectable precancerous lesions, although persistent oral infection and HPV-positive oropharyngeal cancer is not as tightly linked as that for anogenital infection and premalignant disease.

In clinical vaccine efficacy trials, the development of premalignant disease and genital warts has been used as primary endpoint for young adults. Licensure trials for the vaccination of young adolescents have been based on immunobridging. A review of scientific evidence concluded that persistent HPV infection of 6 months or longer can be used as an appropriate endpoint in the evaluation of protection against cervical and anal infections in individuals 16-26 years old (Table 2.2.1) [118].

For the evaluation of vulvar/vaginal protection, HPV16/18-positive high-grade intraepithelial neoplasia (VIN/VAIN) is recommended as an endpoint, owing to relatively little experience with persistent HPV infection as a surrogate endpoint for these diseases. Because of the lack of detectable precancerous lesions for oropharyngeal cancers, the only feasible endpoint is persistent HPV16/18 infection, but the relationship between persistent oral infection and HPV-positive oropharyngeal cancer is not as tightly linked as that for anogenital infections and premalignant disease [118, 119].

To evaluate the duration of protection, new administration schemes and programme strategies, the routine use of virological and immunogenicity endpoints would be feasible with the availability of a set of internationally recognized standards [118].

Table 2.2.1 Recommendations for vaccine endpoints by age group for cervical, vulvar/vaginal, anal and oral sites and for different scenarios [118]

Age group	Immunobridging	Protection at anatomical site			
		Cervical	Vulvar/ vaginal	Anal	Oral
Placebo-controlled trial of a licensed HPV VLP vaccine: three doses					
<16 years	Non-inferiority to the established dosing regimen in the population in which efficacy was demonstrated (typically, individuals aged 16-26 years) for each vaccine HPV type	NA	NA	NA	NA
16-26 years	NA	Persistent infection with vaccine HPV types[b]	High-grade VIN/VAIN	Persistent infection with vaccine HPV types[b]	Persistent HPV16/18 infection[b]
>26 years	NA	Persistent infection with vaccine HPV types[b] or disease (CIN2+)	High-grade VIN/VAIN	Persistent infection with vaccine HPV types[b] or disease e(AIN)	Persistent HPV16/18 infection[b]
Development of a new HPV VLP vaccine similar to the licenced product or products: three doses					
<16 years	Non-inferiority to immunity in the age group 16–26 years for each vaccine HPV type[c]	NA	NA	NA	NA
16-26 years	Non-inferiority for each vaccine HPV type compared with a licensed product[d]	Post-licensure: confirm efficacy with vaccine HPV types using virological and/or disease end-points	NA	NA	NA
>26 years	NA	Persistent infection with vaccine HPV types[b] or disease (CIN2+)	High-grade VIN/VAIN	Persistent infection with vaccine HPV types[b] or disease (AIN)	Persistent HPV16/18 infection[b]
Development of a new polyvalent VLP vaccine containing additional HPV types compared with a licensed product or products: three doses					
<16 years	Non-inferiority to the established dosing regimen in the population in which efficacy was demonstrated (typically, individuals aged 16–26 years) for each vaccine HPV type	NA	NA	NA	NA
16-26 years	Non-inferiority for each HPV type shared by both vaccines	Composite end-point of persistent infection with new HPV types[e,b]	High-grade HPV16/18 VIN/VAIN	Composite end-point of persistent infection with new HPV types[e,b]	Persistent HPV 16/18 infection[b]
>26 years	NA	Persistent infection with vaccine HPV types[e,b] or disease (CIN2+)	High-grade HPV16/18 VIN/VAIN	Persistent infection with vaccine HPV types[e,b] or disease (AIN)	Persistent HPV16/18 infection[b]

Age group	Immunobridging	Protection at anatomical site			
		Cervical	Vulvar/ vaginal	Anal	Oral
One or two doses for an HPV VLP vaccine approved for three doses, in situations in which immunological non-inferiority can be demonstrated					
<16 years	Non-inferiority to the standard three-dose schedule in the population in which efficacy was demonstrated (typically, individuals aged 16–26 years) for each vaccine HPV type[e,f]	NA	NA	NA	NA
16-26 years	Non-inferiority to the standard three-dose schedule in the population in which efficacy was demonstrated (typically, individuals aged 16–26 years) for each vaccine HPV type[e,f]	NA	NA	NA	NA
>26 years	NA	Persistent infection with vaccine HPV types[f,b] or disease (CIN2+)	High-grade HPV16/18 VIN/VAIN	Persistent infection with vaccine HPV types[f,b] or disease (AIN)	Persistent HPV16/18 infection[b]
One or two doses for an HPV VLP vaccine approved for three doses: alternative approach for situations in which immunologic non-inferiority cannot be demonstrated					
<16 years	Non-inferiority to the established dosing regimen in the population in which efficacy was demonstrated (typically, individuals aged 16–26 years) for each vaccine HPV type	NA	NA	NA	NA
16-26 years	NA	Composite end-point of persistent infection with vaccine HPV types[b,e,f,g]	High-grade HPV16/18 VIN/VAIN	Composite endpoint of persistent infection with vaccine HPV types[b,e,f,g]	Persistent HPV16/18 infection[b]
>26 years	NA	Composite persistent infection with vaccine HPV types[b,e,f,g] or disease (CIN2+)	High-grade HPV16/18 VIN/VAIN	Composite persistent infection with vaccine HPV types[b,e,f,g] or disease (AIN)	Persistent HPV16/18 infection[b]

AIN, anal intraepithelial neoplasia; CIN2+, cervical intraepithelial neoplasia of grade 2 or worse; NA, not applicable; VIN/VAIN, vulvar intraepithelial neoplasia/vaginal intraepithelial neoplasia; VLP, virus-like particle.

[a] In most countries, it is probably not ethical to have a placebo group in view of the fact that regulatory authorities in many countries have already licensed the vaccine for the age groups in question. Recommended only if a national regulatory authority requires a placebo-controlled trial.

[b] 6 months or longer.

[c] Immunobridging can be done in the age group < 16 years if immunological non-inferiority for each vaccine HPV type has been demonstrated for the age group 16–26 years.

[d] A virological endpoint would be required if non-inferiority could not be demonstrated.

[e] Monitor vaccine efficacy against each HPV type.

[f] Post-licensure: confirm long-term efficacy against composite persistent infection and/or disease for vaccine HPV types.

[g] The comparison group for establishing efficacy should be agreed upon in advance with regulatory authorities. Because the attack rate for persistent infection in, for example, both a two-dose and a three-dose group is expected to be very low, demonstrating non-inferiority for this endpoint may not

be feasible. Such a situation may require the exploration of alternative approaches for demonstrating efficacy, such as the use of historical controls or the use of concurrently collected prevalence data from the broader population within which the study is conducted. Post-licensure: confirm long-term efficacy against composite persistent infection and/or disease for vaccine HPV types.

[h] Post-licensure: confirm long-term efficacy for infection and/or disease endpoints.

[i] For non-VLP vaccine candidates, it may be acceptable to infer efficacy based on the demonstration of immunological non-inferiority compared with a licensed VLP vaccine. The acceptability of this approach should be determined on a case-by-case basis, taking into account the product itself and whether preclinical data suggest that the mechanism of protection is expected to be similar to that for VLP-based vaccines. This table addresses situations in which demonstration of immunological non-inferiority compared with a licensed vaccine is either not possible or has been determined to be an unacceptable approach to demonstrating efficacy.

The comparison group for establishing efficacy should be agreed upon in advance with regulatory authorities. Because the attack rate for persistent infection in both the licensed vaccine and the candidate vaccine groups is expected to be very low, demonstrating non-inferiority for this endpoint may not be feasible. Such a situation may require the exploration of alternative approaches for demonstrating efficacy, such as the use of historical controls or the use of concurrently collected prevalence data from the broader population within which the study is conducted.

2.3 Vaccine efficacy and effectiveness

Summary

In HPV-DNA negative and HPV16/18 naïve women, high vaccine efficacies (VE) were found against incident (94%) and prevalent (89.4%) HPV16/18 infection. Similar VEs were found for 2vHPV, 4vHPV and 9vHPV against persistent cervical infection and atypical squamous cell of undetermined significance or worse (ASC-US+). The VE against vaccine type related CIN in HPV- or TVC-naïve women ranged from 96.5% for low grade CIN, to 100% for high grade CIN. The VE against AIS related to vaccine type in HPV- or TVC-naïve women was 100% for both 2vHPV and 4vHPV. VE against vaccine type related non-cervical endpoints for both 2vHPV and 4vHPV among HPV-naïve was high. For anal and oral infections, the VE of the 2vHPV was 83% and 93%, respectively. Against VIN and VaIN, the VE was 100% for the 4vHPV. For the 4vHPV vaccine, VE against genital warts related to vaccine types was 100%.

Among HPV naïve males, the VE for the 4vHPV vaccine against vaccine-type-related genital warts and external genital lesions was respectively 90% and 91%. Among MSM, efficacy against type-specific DNA positivity at the anus and AIN was also found for the 4vHPV vaccine of 84.0% and 77.5%, respectively.

For the bivalent vaccine, significant cross-protection was found for persistent infections with HPV types 31, 33, 45 and 51. For the quadrivalent vaccine, cross-protective vaccine efficacy was found against HPV31.
Immunogenicity data was used to bridge clinical vaccine efficacy in individuals older than 15 to younger age groups, the other gender and reduced dose schedules. High and sustained antibodies were found for the bivalent vaccine, the quadrivalent vaccine and the nonavalent vaccine up to 9, 9 and 3.5 years after vaccination, respectively. Lower, but non-inferior geometric mean titres (GMT) were found after two-dose schedules (9-14 years) than were found after three-dose schedules (>15 years). Avidity was comparable between both schedules.
Various countries showed high vaccine effectiveness after the introduction of HPV vaccination against HPV infections, genital warts and cervical abnormalities. For the Netherlands, high vaccine effectiveness 2vHPV is found against both incident and persistent infections up to five years post-vaccination for both vaccine types (HPV16/18) and including cross-protective types (HPV31/45). VE against persistent HPV16/18 infections was 100% and 89% when including cross-protective types HPV31/45 among girls naïve for these types before vaccination.
A biennial study conducted among STI-clinic visitors found that the percentage of women testing positive for HPV16 and/or HPV18 decreased from 23% in 2009, before vaccination was implemented, to 15% in 2015. Among heterosexual men, there was also a decreasing trend in the percentage testing positive for HPV16 and/or HPV18 (from 17% in 2009 to 11% in 2015), suggesting possible herd immunity resulting from girls' vaccination. Among vaccine eligible-women visiting the STI clinic, the effect of the bivalent HPV-16/18 vaccine on genital HPV-6/11 positivity and anogenital warts was studied, but no impact was found.

2.3.1 Vaccine efficacy (VE)

2.3.1.1 Females

Several studies provided data on the efficacy of the HPV vaccines against HPV infection and associated diseases in women. The most important trials assessed three doses of the 2vHPV or 4vHPV vaccine, administered at 0, 1 or 2 and 6 months. This section describes the included studies. The following sections provide an overview of the efficacy with respect to different endpoints. The populations analysed in the studies included are described in Appendix A.

The efficacy of 2vHPV was assessed in the HPV-001/007/023 trial, the PApilloma TRIal against Cancer In young Adults (PATRICIA), the Costa Rica HPV-16/18 Vaccine Trial (CVT, the only prelicensing trial not funded by industry) and the Human PapillomaVIrus: Vaccine Immunogenicity ANd Efficacy (VIVIANE) trial [120, 121]. In the FUTURE I/II trials, the efficacy of 4vHPV was assessed.

The HPV-001/007/023 trial with the two-valent vaccine was conducted in the US, Canada and Brazil in healthy women aged 15-25 years with no known history of HPV infection or disease. It started with the HPV-001 trial with 1,113 participants and a follow-up of 27 months, and ended with the HPV-023 trial, which assessed the efficacy of the 2vHPV vaccine up to 9.4 years after the first vaccination (n=437 participants).

The PATRICIA-trial (with 2vHPV and a follow-up of four years) was conducted in 14 countries in Europe, North and South America, Asia and Australia (*N* = 18,644). Healthy women aged 15–25 years-old were enrolled, regardless of HPV DNA status, HPV serostatus or cervical cytology at baseline.

The CVT-trial was conducted in healthy Costa Rican women aged 18–25 years, irrespective of past sexual behaviour, HPV status or cytology (*N* = 7,466). Analyses on the efficacy of the 2vHPV vaccine were available from four years after the first vaccination.

The VIVIANE-trial with 2vHPV was conducted in 12 countries in Europe, Australia, Southeast Asia, and North and South America (*N* = 5,752) and enrolled women older than 25 years, irrespective of past sexual behaviour, cytology, HPV serostatus or DNA status. An interim analysis presented the efficacy of the 2vHPV vaccine four years after the first vaccination had been reported.

The FUTURE I/II trials enrolled women from all over the world and assessed the efficacy of the 4vHPV vaccine [122, 123]. The trials were conducted in 17,622 women aged 16-26 years. Women with a history of an abnormal Pap test, a history of genital warts or a detection of genital warts at enrolment were excluded. The average follow-up period was approximately 3.6 years.

One study assessed the efficacy of 9vHPV vaccine to prevent HPV-related cervical, vulvar and vaginal disease using 4vHPV vaccine as a comparator. This trial included 16 to 26-year-old girls and women (9vHPV = 7,099; 4vHPV = 7,105) who were enrolled and vaccinated without pre-screening for the presence of HPV infection. The subjects were followed for a median duration of 40 months (range of 0 to 64 months) after the last vaccination [124, 125].

Several other papers about the efficacy of HPV vaccines have been published, but these papers are based on the afore mentioned studies or are based on a relatively short follow-up period. These papers are therefore not included in the present overview, although some of them

are included in the meta-analysis of Deleré et al [126]. The results of these studies are in accordance with the results of the trials we included here.

2.3.1.1.1 Cervix

Table 2.3.1 shows the VE against incident and prevalent HPV-16/18 infection. High VEs were found in HPV-negative and HPV16/18-naïve populations. In women previously exposed to HPV, somewhat lower VE was found (76.5% (95%CI 54.6-88.8).

Table 2.3.1 VE against incident and prevalent HPV-16/18 infection

Endpoint	Vaccine	Analysis populationa	Age	Follow-up	Vaccine efficacy (95% CI)	Source
Incident infection	2vHPV	HPV-negative	9-26 years	=<5 years >5 years	83 (70-90) 94 (80-98)	Meta-analysis [126]
Prevalent infection	2vHPV	Full cohort TVC-naïve TVC-previously exposed	18-25 years	4 years	76.4 (66.9-83.4) 89.4 (79.0-95.2) 76.5 (54.6-88.8)	CVT-trial [40]

[a] Description of the analysis population: see Appendix A
CI = confidence interval; CVT = Costa Rica Vaccine Trial; TVC = total vaccinated cohort.

Table 2.3.2 provides an overview of studies that assess the VE against persistent cervical infection and ASC-US+ associated with HPV16/18. Most information is available for the bivalent vaccine and shows a VE of about 90% or higher in different study groups. Only in the TVCE was a lower VE found (80.4%, 95% CI 70.4-87.4). The VE against at least a six month persistent infection related to HPV types 31, 33, 45, 52, 58 of 9vHPV, compared to 4vHPV, was 96.0% (95%CI 94.4-97.2).

Table 2.3.2 VE against persistent cervical infection and atypical squamous cell of undetermined significance or worse (ASC-US+) associated with HPV infection

Endpoint	Vaccine	Analysis population[a]	Age	Follow-up	Vaccine efficacy (95% CI)	Source
6 months persistent related to HPV16/18	2vHPV	ATP cohort	15-25 yrs	39.4 months	93.8 (91.0-95.9)	Patricia [121]
		ATP-cohort	>25 yrs	84 months	91.4 (79.4-97.1)	Viviane [127]
		TVC	15-25 yrs	6.4 yrs	94.4 (78.2-99.4)	001/007/023 [121]
		TVC-naïve	15-25 yrs	4 yrs	93.7 (91.1-95.6)	Patricia [121]
		TVCE	15-25 yrs	14.8 months	80.4 (70.4-87.4)	Patricia [121]
		TVCE	>25 yrs	84 months	88.1 (76.1-94.7)	Viviane [127]
	2vHPV/4vHPV	HPV-negative	9-26 yrs	=<5 yrs	90 (79-95)	Meta-analysis [126]
		HPV-negative	9-26 yrs	>5 yrs	95 (84-99)	Meta-analysis [126]
6 months persistent related to HPV31,33,45,52,58	9vHPV	PP	16-26 yrs	54 months	96.0 (94.4-97.2)[b]	Joura, 2015 [125]
6 months persistent related to HPV6,11,16,18	9vHPV	PP	16-26 yrs	54 months	26. 4 (-4.3-47.5)[b]	Joura, 2015 [125]
12 months persistent	2vHPV	ATP cohort	18-25 yrs	4 yrs	90.9 (82.0-95.9)	CVT-trial [121]
		HPV negative	18-25 yrs	4 yrs	88.6 (77.3-94.9)	CVT-trial [121]
ASC-US+	2vHPV	ATP cohort	15-25 yrs	18-27 months	93.5 (51.3-99.1)	001/007/023 [121]
		ATP cohort	>25 yrs	84 months	93.8 (79.9-98.9)	Viviane [127]
		TVC	15-25 yrs	18-27 months	97.1 (82.5-99.9)	001/007/023 [121]
		TVCE	>25 yrs	84 months	89.2 (73.9-96.4)	Viviane [127]

[a] Description of the analysis population: see Appendix A
[b] Compared to the 4vHPV vaccine
ATP = according-to-protocol; CI = confidence interval; CVT = Costa Rica Vaccine Trial; TVC = total vaccinated cohort; TVCE = total vaccinated cohort for efficacy; PP = per-protocol.

Several trials assessed the VE of 2vHPV and 4vHPV against low-grade CIN in different study groups (see Table 2.3.3). For both vaccines, the VE against CIN1 and CIN1+ related to vaccine types was approximately 84% or higher in most study groups. In the intention-to-treat (ITT) population, VEs against CIN1 (4vHPV) and CIN1+ (2vHPV) related to vaccine types were 67.5% (95%CI 59.1-74.4) and 62.9% (95%CI 54.1-70.1), respectively. The VEs for CIN1 and CIN1+, independent of HPV type, were about half the vaccine type-specific VE and higher for the 2vHPV than the 4vHPV.

Table 2.3.3 VE against CIN1 or CIN1+

Endpoint	Vaccine	Analysis population[a]	Age	Follow-up	Vaccine efficacy (95% CI)	Source
CIN1 vaccine type	4vHPV	HPV-naïve	16-26 yrs	Mean 3.6 yrs	97.2 (91.5-99.4)	FUTURE I/II [128, 129]
		ITT	16-26 yrs	Mean 3.6 yrs	67.5 (59.1-74.4)	
CIN1 independent of type	4vHPV	HPV-naïve	16-26 yrs	Mean 3.6 yrs	29,7 (16.9-40.6)	FUTURE I/II [128, 129]
		ITT	16-26 yrs	Mean 3.6 yrs	20.3 (12.4-27.5)	
CIN1+ vaccine type	2vHPV	ATP cohort	>25 yrs	84 months	83.7 (21.9-98.5)	Viviane [127]
		TVC	15-25 yrs	9.4 yrs	100 (45.2-100)	001/007/023 [121]
		TVC-naïve	15-25 yrs	4 yrs	96.5 (91.6-98.9)	Patricia [121]
		TVCE	15-25 yrs	14.8 yrs	89.2 (59.4-98.5)	Patricia [121]
		TVCE	>25 yrs	84 months	75.5 (19.8-94.5)	Viviane [127]
		ITT	15-25 yrs	4 yrs	62.9 (54.1-70.1)	Patricia [129]
	4vHPV	ATP cohort	16-24 yrs	36 months	95.8 (87.2-99.2)	FUTURE I/II [130]
CIN1+ independent of type	2vHPV	TVC-naïve	15-25 yrs	4 yrs	50.3 (40.2-58.8)	Patricia [129]
		ITT	15-25 yrs	4 yrs	27.7 (19.5-35.2)	Patricia [129]
	4vHPV	HPV-naïve	16-26 yrs	Mean 3.6 yrs	29.7 (17.7-40.0)	FUTURE I/II [128, 129]
		ITT	16-26 yrs	Mean 3.6 yrs	19.1 (11.9-25.7)	FUTURE I/II [128, 129]

[a] Description of the analysis population: see Appendix A
ATP = according-to-protocol; CI = confidence interval; CIN = cervical intraepithelial neoplasia; ITT = intention-to-treat; TVC = total vaccinated cohort; TVCE = total vaccinated cohort for efficacy.

The VEs against CIN2 or CIN2+ related to vaccine types were comparable to the VEs against CIN1 and CIN1+ in the different populations (see Table 2.3.4). For the ITT population, lower VEs against CIN2 and CIN2+ related to vaccine types were found. As with CIN1 and CIN1+, independent of HPV type, the VEs for CIN2 and CIN2+, independent of HPV type, were lower, but less pronounced than with CIN1 and CIN1+, but again higher for 2vHPV than for 4vHPV. The nonavalent vaccine showed the same efficacy against CIN2+ related to HPV6, -11, -16, -18 when compared to 4vHPV (-0.4%; 95%CI ≤-999-97.4), although the power of this subgroup analysis is low.

Table 2.3.4 VE against CIN2 or CIN2+

Endpoint	Vaccine	Analysis population[a]	Age	Follow-up	Vaccine efficacy (95% CI)	Source
CIN2 vaccine type	4vHPV	HPV-naïve	16-26 yrs	Mean 3.6 yrs	100 (91.4-100)	FUTURE I/II [128, 129]
		ITT	16-26 yrs	Mean 3.6 yrs	53.0 (38.2-64.5)	FUTURE I/II [128, 129]
CIN2 independent of type	4vHPV	HPV-naïve	16-26 yrs	Mean 3.6 yrs	42.9 (20.2-59.5)	FUTURE I/II [128, 129]
		ITT	16-26 yrs	Mean 3.6 yrs	19.3 (5.7-31.0)	FUTURE I/II [128, 129]
CIN2+ vaccine type	2vHPV	ATP cohort	>25 yrs	84 months	100 (-100.7-100)	Viviane [127]
		ATP cohort	15-25 yrs	4 yrs	94.9 (87.7-98.4)	Patricia [121]
		ATP cohort	18-25 yrs	4 yrs	89.8 (39.5-99.5)	CVT [121]
		TVC	15-25 yrs	9.4 yrs	89.8 (39.5-99.5)	001/007/023 [121]
		TVC-naïve	15-25 yrs	4 yrs	99.0 (94.2-100)	Patricia [121]
		HPV-negative	18-25 yrs	4 yrs	100 (54.7-100)	CVT [121]
		TVCE	>25 yrs	84 months	80.4 (-125.3-99.8)	Viviane [127]
		TVCE	15-25 yrs	39.4 months	94.5 (86.2-98.4)	Patricia [121]
		ITT	15-25 yrs	4 yrs	60.7 (49.6-69.5)	Patricia [129]
	4vHPV	ATP-cohort	16-24 yrs	36 months	100 (89.8-100.0)	FUTURE I/II [130]
	2vHPV/4vHPV	HPV-negative	9-26 yrs	≤5 yrs	84 (50-95)	Meta-analysis [126]
		HPV-negative	9-26 yrs	>5 yrs	86 (-166-99)	Meta-analysis [126]
CIN2+ related to HPV-31,33,45,52,58	9vHPV	ITT	16-26 yrs	54 months	19.0 (-1.6-35.3)[b]	Joura, 2015 [125]
		PP	16-26 yrs	54 months	96.3 (79.5-99.8)[b]	Joura, 2015 [125]
CIN2+ related to HPV-6,11,16,18	9vHPV	PP	16-26 yrs	54 months	-0.4 (≤-999-97.4)[b]	Joura, 2015 [125]
CIN2+ independent of type	2vHPV	TVC-naïve	15-25 yrs	4 yrs	64.9 (52.7-74.2)	Patricia [129]
		ITT	15-25 yrs	4 yrs	33.1 (22.2-42.6)	Patricia [129]
	4vHPV	HPV-naïve	16-26 yrs	Mean 3.6 yrs	42.7 (23.7-57.3)	FUTURE I/II [128, 129]
		ITT	16-26 yrs	Mean 3.6 yrs	19.0 (7.7—28.9)	FUTURE I/II [128, 129]

[a] Description of the analysis population: see Appendix A
[b] Compared to 4vHPV
ATP = according-to-protocol; CI = confidence interval; CIN = cervical intraepithelial neoplasia; CVT = Costa Rica Vaccine Trial; ITT = intention-to-treat; TVC = total vaccinated cohort; TVCE = total vaccinated cohort for efficacy; PP = per-protocol.

Table 2.3.5 shows the VE against CIN3 and CIN3+. For 4vHPV and 2vHPV, high VEs against CIN3 related to vaccine type were found in the per-protocol populations. Among baseline HPV-negative females, VEs against CIN3, irrespective of HPV type, are 93.2% and 43.0% for 2vHPV and 4vHPV vaccines, respectively. In the intention-to-treat populations, lower VEs were reported.

Table 2.3.5 VE against CIN3 or CIN3+

Endpoint	Vaccine	Analysis population[a]	Age	Follow-up	Vaccine efficacy (95% CI)	Source
CIN3 vaccine type	4vHPV	HPV-naïve	16-26 yrs	Mean 3.6 yrs	100 (90.5-100)	FUTURE I/II [128, 129]
		ITT	16-26 yrs	Mean 3.6 yrs	43.5 (27.3-56.2)	FUTURE I/II [128, 129]
CIN3 independent of type	2vHPV	TVC-naïve	15-25 yrs	4 yrs	93.2 (78.9-97.7)	Patricia [129]
		ITT	15-25 yrs	4 yrs	45.6 (28.8-58.7)	Patricia [129]
	4vHPV	HPV-naïve	16-26 yrs	Mean 3.6 yrs	43.0 (13.0-63.2)	FUTURE I/II [128, 129]
		ITT	16-26 yrs	Mean 3.6 yrs	16.4 (0.4-30.0)	FUTURE I/II [128, 129]
CIN3+ vaccine type	2vHPV	ATP cohort	15-25 yrs	4 yrs	91.7 (66.6-99.1)	Patricia [121]
		TVC-naïve	15-25 yrs	4 yrs	100 (85.5-100)	Patricia [121]
		TVCE	15-25 yrs	39.4 months	90.9 (60.8-99.1)	Patricia [121]
		ITT	15-25 yrs	4 yrs	45.7 (22.9-62.2)	Patricia [129]
	4vHPV	ATP-cohort	16-24 yrs	36 months	100 (<0.0-100)	FUTURE I/II [130]
	2vHPV/4vHPV	HPV-negative	9-26 yrs	<5 yrs	94 (83-98)	Meta-analysis [126]

[a] Description of the analysis population: see Appendix A
ATP = according-to-protocol; CI = confidence interval; CIN = cervical intraepithelial neoplasia; ITT = intention-to-treat; TVC = total vaccinated cohort; TVCE = total vaccinated cohort for efficacy.

The VE against AIS related to vaccine type ranged from 60.0 to 100% in the different study groups, although the confidence intervals are wide. Comparable results were found for AIS, independent of vaccine type.

Table 2.3.6 VE against adenocarcinoma in situ (AIS)

End-point	Vaccine	Analysis population[a]	Age	Follow-up	Vaccine efficacy (95% CI)	Source
AIS - vaccine type	2vHPV	ATP-E	15-25 yrs	4 yrs	100 (-8.6-100)	Patricia [131]
		TVC	15-25 yrs	4 yrs	70.0 (-16.6-94.7)	Patricia [131]
		TVC-naïve	15-25 yrs	4 yrs	100 (15.5-100)	Patricia [131]
	4vHPV	HPV-naïve	16-26 yrs	Mean 3.6 yrs	100 (<0-100)	FUTURE I/II [128, 129]
		ITT	16-26 yrs	Mean 3.6 yrs	60.0 (<0-87.3)	FUTURE I/II [128, 129]
AIS independent of type	2vHPV	TVC	15-25 yrs	4 yrs	76.9 (16.0-95.8)	Patricia [131]
		TVC-naïve	15-25 yrs	4 yrs	100 (31.0-100)	Patricia [131]
	4vHPV	HPV-naïve	16-26 yrs	Mean 3.6 yrs	100 (<0-100)	FUTURE I/II [128, 129]
		ITT	16-26 yrs	Mean 3.6 yrs	62.5 (<0-88.0)	FUTURE I/II [128, 129]

[a] Description of the analysis population: see Appendix A
AIS = adenocarcinoma in situ; ATP = according-to-protocol; CI = confidence interval; ITT = intention-to-treat; TVC = total vaccinated cohort.

2.3.1.1.2 Anal infections

Data on protection against infections and disease at the anatomical site of the anus in females is limited to the efficacy against HPV16/18 prevalent infections of the bivalent vaccine (Table 2.3.7). These efficacies were calculated in the CVT study conducted among 18 to 25-year-old females, with a follow-up of four years. In the total cohort, the vaccine efficacy against HPV16/18 anal HPV infections was above 62%. In the HPV naïve population, the VE was above 83% [40, 132]. No efficacy studies regarding anal infection in women were found available for the quadrivalent and the nonavalent vaccine.

Table 2.3.7 VE of the bivalent vaccine against prevalent HPV16/18 anal infection in women (18-25 years of age)

Analysis population[a]	Vaccine efficacy (95% CI)	Source
TVC	62.1 (47.3-73.1)	CVT [40]
	62.0 (47.1-73.1)	CVT [132]
HPV-naïve	85.1 (68.4-93.8)	CVT [40]
	83.6 (66.7-98.7)	CVT [132]
TVC-Previously exposed	54.4 (22.4-73.9)	CVT [40]
TVC-Currently exposed	25.3 (-40.4-61.1)	CVT [40]

[a] Description of the analysis population: see Appendix A
CI = confidence interval; CVT = Costa Rica Vaccine Trial; TVC = total vaccinated cohort.

Kreimer et al. also explored the VE of the bivalent vaccine against anal HPV infections related to HPV31/33/45. For the full cohort, the VE was 49.4% (95% CI 30.3-63.6%) and, in the restricted cohort (HPV naïve and completely vaccinated), the VE was 61.8% (95% CI 42.8-75.0%) [132]. The cross-protection of the vaccines is described in greater detail in Chapter 2.3.2.

2.3.1.1.3 Oropharyngeal infections

Data on protection against infections and disease at the oropharynx in females is limited to the efficacy of the bivalent vaccine against oral prevalent infections (Table 2.3.8). The VE for vaccine types was above 90% and was calculated in the Costa Rica trial in the full cohort among 18 to 25-year-old females, with a follow-up of four years [40, 133].

Table 2.3.8 VE of the bivalent vaccine against prevalent HPV16/18 oral infection in women (18-25 years of age)

Endpoint	Vaccine efficacy (95% CI)	Source
Oral infection with HPV16/18	100.0 (60.5-100.0) 93.3 (63-100)	CVT [40] CVT [133]
Oral infection with HPV16	91.6 (51.7-99.6)	CVT [133]
Oral infection with HPV18	100 (-12-100)	CVT [133]
Oral infection with oncogenic types	45.7 (6.9-69.0)	CVT [133]
Oral infection with oncogenic types without HPV16/18	13.2 (-61.1-53.6)	CVT [133]

CI = confidence interval; CVT = Costa Rica Vaccine Trial.

Herrero et al. also estimated the VE for oral prevalent infections against other oncogenic types. Although the point estimates were above 0%, the confidences were very wide and no statistically significant protection provided by the bivalent vaccine could be shown against HPV31/51/52/56/39. The overall VE against oncogenic types combined was 45.7% (95% CI 6.9-69.0%), excluding HPV16/18, which was estimated at 13.2% (95% CI -61.1-53.6%) [133]. The cross-protection of the vaccines is described in greater detail in Chapter 2.3.2.

2.3.1.1.4 Genital warts

Data on protection against genital warts in terms of vaccine efficacy is limited to the quadrivalent vaccine. For vaccine types in the HPV naïve/per protocol analysis population, the VE was above 97%. The VE against genital warts for any HPV type was 82.8% (95% CI 74.3-88.8%) [128, 129, 132, 134].

Table 2.3.9 VE of the quadrivalent vaccine against genital warts in women

Endpoint	Analysis populationa	Age	Folow-up	Vaccine efficacy (95% CI)	Source
Genital warts vaccine types	HPV-naïve	16-26 years	3.6 years (mean)	97.1 (92.4-99.2)	FutureI/II [128, 129]
	ITT	16-26 years	3.6 years (mean)	79.3 (72.7-84.5)	FutureI/II [128, 129]
	mITT	16-23 years	5 years	100 (<0-100)	Villa et al [134]
	PP	16-23 years	5 years	100 (<0-100)	
Genital warts any type	HPV-naïve	16-26 years	3.6 years (mean)	82.8 (74.3-88.8)	FutureI/II [128, 129]
	ITT	16-26 years	3.6 years (mean)	62.0 (53.5-69.1)	FutureI/II [128, 129]

[a] Description of the analysis population: see Appendix A
CI = confidence interval; ITT = intention-to-treat; PP = per-protocol.

2.3.1.1.5 Vulva

Reporting of vaccine efficacy against VIN and/or vulvar cancer was limited to the quadrivalent vaccine (Table 2.3.10). For the bivalent vaccine, a VE among sexually active participants of the Costa Rica Vaccine Trial against prevalent vulvar infections of 54.4% (95% CI 4.9-79.1%) was calculated [135]. For the quadrivalent vaccine against both VIN1 and VIN2/3 related to vaccine types, the VE was 100%. In the ITT population, the efficacy against VIN1 and VIN2/3 was, respectively, 69.1% (95% CI 29.8-87.9%) and 73.3% (95% CI 40.3-89.4%) [136, 137].

Table 2.3.10 Efficacy of the bivalent and quadrivalent vaccines against VIN

Endpoint	Vaccine	Analysis population [a]	Age	Follow-up	Vaccine efficacy (95% CI)	Source
Vulvar infection of any type	Bivalent	Sexually actives who supplied vulvar swab	18-25 years	Four years	54.1 (4.9-79.1)	CVT [135]
VIN1 vaccine type	Quadrivalent	PP ITT Unrestricted susceptible	16-26 years 16-26 years 16-26 years	42 months 42 months 42 months	100 (74.1-100) 69.1 (29.8-87.9) 89.9 (58.6-98.9)	Future I/II [137] Future I/II [137] Future I/II [137]
VIN1 any type	Quadrivalent	HPV naïve ITT	16-26 years 16-26 years	42 months 42 months	74.7 (21.5-93.8) 32.3 (<0-60)	Future I/II [137] Future I/II [137]
VIN2/3 vaccine types	Quadrivalent	PP ITT	16-26 years 16-26 years	3.6 years 3.6 years	100 (67.2-100.0) 73.3 (40.3-89.4)	Future I [116] Future I [116]

[a] Description of the analysis population: see Appendix A
CI = confidence interval; ITT = intention-to-treat; PP = per-protocol; VIN = vulvar intraepithelial neoplasia.

2.3.1.1.6 Vagina

Reporting of vaccine efficacy against VaIN and/or vaginal cancer was limited to the quadrivalent vaccine [138]. For the quadrivalent against both VaIN1 and VaIN2/3 related to vaccine types, the VE was 100% in the PP population. In the ITT population, the efficacy against vaccine types VaIN1 and VaIN2/3 was, respectively, 83.3% (95% CI 51.3-95.8%) and 85.7% (95% CI 37.6-98.4%) [136, 137].

Table 2.3.11 Efficacy of the quadrivalent vaccine against VaIN

Endpoint	Analysis population[a]	Age	Follow-up	Vaccine efficacy (95% CI)	Source
VaIN1 vaccine type	PP ITT Unrestricted susceptible	16-26 yrs 16-26 yrs 16-26 yrs	42 months 42 months 42 months	100 (64.0-100) 83.3 (51.3-95.8) 100.0 (77.1-100)	Future I/II ([137] Future I/II [137] Future I/II [137]
VaIN1 any type	HPV-naïve ITT	16-26 yrs 16-26 yrs	42 months 42 months	48.1 (10.2-70.9) 30.9 (3.5-50.8)	Future I/II [137] Future I/II [137]
VaIN2/3 vaccine types	PP ITT	16-26 yrs 16-26 yrs	3.6 yrs 3.6 yrs	100 (55.4-100.0) 85.7 (37.6-98.4)	Combined protocols [116] Combined protocols [116]

[a] Description of the analysis population: see Appendix A
CI = confidence interval; ITT = intention-to-treat; PP = per-protocol; VaIN = vaginal intraepithelial neoplasia.

2.3.1.1.7 Combined endpoints

For both the quadrivalent and nonavalent vaccines, the efficacies have also been reported on combined endpoints (of multiple anatomical sites) (Table 2.3.12). Against VIN and VaIN grades two and three related to vaccine types, the quadrivalent vaccine showed an efficacy of over 75% in both the intention-to-treat as in the HPV-naïve analysis population [128]. The nonavalent vaccine showed an efficacy (with quadrivalent vaccine as comparator) of 100% (95%CI 70.4-100.0%) against CIN,

VIN and VaIN related to vaccine types in the modified intention-to-treat analysis [125].

Table 2.3.12 Efficacy of the quadrivalent and nonavalent vaccines against lesions at multiple anatomical sites in women

Endpoint	Vaccine	Analysis population[a]	Age	Follow-up	Vaccine efficacy (95% CI)	Source
CIN/VIN/VaIN 2/3 any type	Nonavalent*	mITT	16-26 years	54 months	42.5 (7.9-65.9)	Joura, 2015 [125]
CIN/VIN/VaIN 2/3 vaccine types	Nonavalent*	mITT	16-26 years	54 months	100 (70.4-100.0)	Joura, 2015 [125]
CIN/VIN/VaIN 2/3 non-vaccine types	Nonavalent*	mITT	16-26 years	54 months	19.7 (-34.5-52.5)	Joura, 2015 [125]
CIN/VIN/VaIN 2/3 related to HPV31/33/45/52/58	Nonavalent*	PP	16-26 years	54 months	96.7 (80.9-99.8)	Joura, 2015 [125]
CIN/VIN/VaIN 2/3 related to HPV6/11/16/18	Nonavalent*	PP	16-26 years	54 months	66.6 (-203-98.7)	Joura, 2015 [125]
VIN1/VaIN 1 related to HPV16/18	Quadrivalent	HPV naïve ITT	16-26 years 16-26 years	3.6 years 3.6 years	100 (66.8-100.0) 87.5 (58.7-97.6)	FutureI/II [128] FutureI/II [128]
VIN/VaIN 2/3 related to HPV16/18	Quadrivalent	HPV naïve ITT	16-26 years 16-26 years	3.6 years 3.6 years	94.9 (68.3-99.9) 75.6 (48.5-89.6)	FutureI/II [128] FutureI/II [128]
VIN/VaIN 2/3 related to HPV31/33/45/52/58	Nonavalent *	PP	16-26 years	43 months	100 (-71.5-100)	EMA EPAR Gardasil9 [117]

* Vaccine efficacy for the nonavalent vaccine was not estimated against placebo, but rather against an active comparator (quadrivalent vaccine)!
[a] Description of the analysis population: see Appendix A
CI = confidence interval; CIN = cervical intraepithelial neoplasia; ITT = intention-to-treat; PP = per-protocol; VaIN = vaginal intraepithelial neoplasia; VIN = vulvar intraepithelial neoplasia.

2.3.1.2 Males

Information on the efficacy of prophylactic HPV vaccination in males is scarce and limited to the quadrivalent vaccine. All three available publications were based on the same study protocol, namely protocol 020. In total, 4,065 healthy boys and men from 18 countries with a maximum of five sexual partners were included in this study, 3,464 of whom (85%) were subjects aged 16-23 that reported they have had only female sexual partners (further on: heterosexuals) and 602 (15%) of whom were subjects aged 16-26 years that reported they have engaged in insertive or receptive anal intercourse or oral sex with a male partner in the past year (further on: MSM). The vaccinated participants were offered a three-dose schedule (0, 2, 6 months) and the maximum follow-up was 36 months. The ITT population consisted of participants who had received at least one dose of vaccine or placebo and returned for a follow-up visit. The PP population consisted of participants who were seronegative and HPV DNA negative for vaccine types at baseline and remained HPV DNA negative up to 7 months of

follow-up. The HPV-naïve population was HPV DNA negative for HPV6/11/16/18/31/33/35/39/45/52/56/58/59 and seronegative for HPV6/11/16/18 [139-141].

2.3.1.2.1 Genital warts/condyloma acuminata

The efficacy of the quadrivalent HPV vaccine against genital warts/condyloma acuminata related to HPV6/11/16/18 was studied among 2,545 initially HPV-naïve participants, both heterosexual males and MSM. The VE against genital warts related to HPV6/11/16/18 was 89.9% (95% CI 67.3-98.0%) [140]. VE estimates, independent of HPV type, varied between 67.2% in the ITT population and 89.4% in the PP population [139, 140] (Table 2.3.13). Goldstone et al. also estimated the vaccine efficacy against intra-anal condyloma acuminata in HPV-naïve MSM. Overall, the VE was 82.3% (95% CI -46.0-99.6%) and the VE was 100% (95% CI -15.7-100%), respectively, against HPV6/11/16/18-specific intra-anal condyloma acuminata [140]. In the PP analysis conducted by Palefsky et al., the VE against HPV6/11/16/18-associated intra-anal condyloma acuminata among MSM was also 100% (95% CI 8.2-100%) [141].

Table 2.3.13 Efficacy of the quadrivalent HPV vaccine against genital warts in males (16-26 years of age)

Endpoint	Analysis population[a]	Vaccine efficacy (95% CI)	Source
Genital warts related to HPV6/11/16/18	HPV naïve	89.9 (67.3-98.0)	Protocol 020 [140]
Genital warts any type	HPV naïve	85.2 (61.8-95.5)	Protocol 020 [140]
	ITT	67.2 (47.7-80.3)	Protocol 020 [139]
	PP	89.4 (65.5-97.9)	Protocol 020 [139]

[a] Description of the analysis population: see Appendix A
CI = confidence interval; ITT = intention-to-treat; PP = per-protocol.

2.3.1.2.2 Anal HPV infection/ anal intraepithelial neoplasia (AIN)

During the study period, no cases of anal cancer were observed in either the vaccinated or the placebo group, so the VE against anal cancer could not be determined. An overview of VE against anal intraepithelial neoplasia is given in Table 2.3.14. Against vaccine types HPV6/11/16/18, the VE was 50.3% (95% CI 25.6-67.2%) and 77.5% (95% CI 39.6-93.3%), respectively, for the ITT or PP analysis. VE against different grades of lesions, independent of HPV type, was also estimated. In the PP analysis, significant protection against AIN1 and AIN2 was shown, with a VE of 54.9% (95% CI 8.4-79.1%) [140, 141]. The percentage of participants with AIN in the vaccine and the placebo group are shown in Figure 2.3.1 [141]. Furthermore, Goldstone et al. estimated a VE of 91.3% (95% CI 40.9-99.8%) against non-acuminate AIN1 specific for the vaccine types HPV6/11/16/18 [140]. In the original paper, type-specific VE estimates against AIN and anal cancer are also reported, 95%-confidence intervals were very wide and included zero, except for HPV6 (both HPV naïve as ITT) and HPV11 (ITT only).

Table 2.3.14 VE against anal intraepithelial neoplasia among MSM (ages 16-26 years)

Endpoint	Analysis population[a]	Vaccine efficacy (95% CI)	Source
AIN any type	PP	54.9 (8.4-79.1)	Protocol 020 [140, 141]
	ITT	25.7 (-1.1-45.6)	Protocol 020 [140, 141]
AIN HPV6/11/16/18	PP	77.5 (39.6-93.3)	Protocol 020 [141]
	ITT	50.3 (25.6-67.2)	Protocol 020 [141]
AIN HPV16/18	PP	78.6 (-0.4-97.7)	Protocol 020 [141]
	ITT	55.2 (8.5-79.3)	Protocol 020 [141]
AIN HPV31/33/35/39/45/51/52/56/58/59	HPV-naïve	-35.1 (-581-70.9)	Protocol 020 [140]
	ITT	11.8 (-39.3-44.4)	Protocol 020 [140]
AIN1 (no condyloma) any type	HPV-naïve	65.1 (-1.0-95.1)	Protocol 020 [141]
	PP	60.4 (-33.5-90.8)	Protocol 020 [141]
	ITT	43.3 (7.3-66.0)	Protocol 020 [140]
AIN2 any type	PP	75.8 (-16.9-97.5)	Protocol 020 [141]
	ITT	61.9 (21.4-82.8)	Protocol 020 [141]
AIN3 any type	PP	63.7 (-103.0-96.4)	Protocol 020 [141]
	ITT	46.8 (-20.2-77.9)	Protocol 020 [141]

[a] Description of the analysis population: see Appendix A
AIN = anal intraepithelial neoplasia; CI = confidence interval; PP = per-protocol.

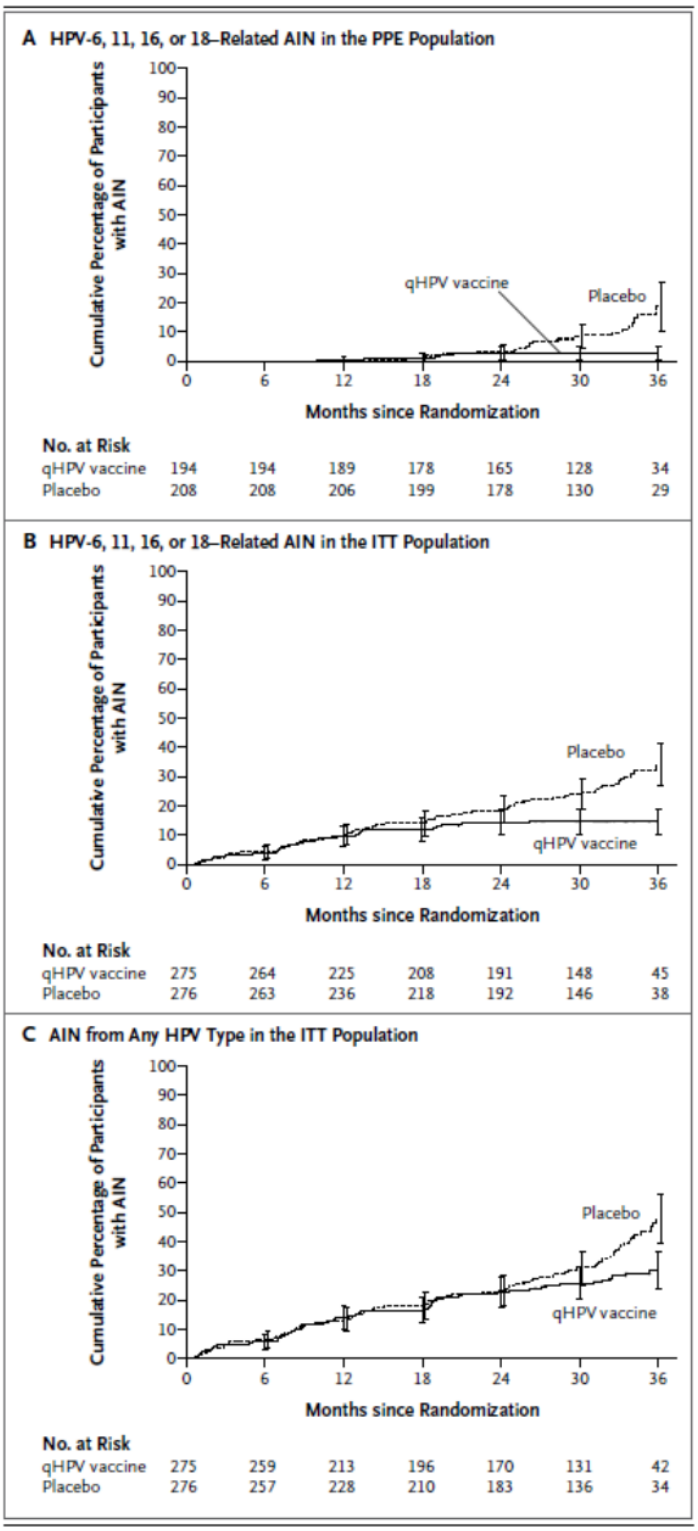

Figure 2.3.1 Cumulative percentages of participants with HPV-related AIN. (from Palefsky et al. 2011) [141]
AIN = anal intraepithelial neoplasia; ITT = intention-to-treat; PP = per-protocol; qHPV = quadrivalent HPV vaccine.

Palefsky et al. estimated the VE against anal infections in MSM, both for HPV DNA detection at any time during the study and for persistent

infection (the same HPV type detected in samples of two or more consecutive visits at least four months apart). In the ITT population, the efficacy was over 45% for HPV DNA detection and over 57% for persistent infections related to vaccine types. For the PP population, the efficacy was over 84% and 94% for DNA detection and persistent infections related to vaccine types, respectively (Table 2.3.15) [141].

Table 2.3.15 VE against anal HPV infections among MSM (16-26 years of age)

Endpoint	Analysis population[a]	Vaccine efficacy (95%CI)	Source
HPV DNA+ HPV6/11/16/18	PP	84.0 (68.6-92.7)	Protocol 020 [141]
	ITT	48.5 (32.3-61.6)	Protocol 020 [141]
HPV DNA+ HPV16/18	PP	84.5 (63.1-94.6)	Protocol 020 [141]
	ITT	46.5 (24.0-62.7)	Protocol 020 [141]
Persistent (4 months) HPV6/11/16/18 infection	PP	94.9 (80.4-99.4)	Protocol 020 [141]
	ITT	59.4 (43.0-71.4)	Protocol 020 [141]
Persistent (4 months) HPV16/18 infection	PP	95.8 (74.1-99.9)	Protocol 020 [141]
	ITT	57.5 (33.2-73.6)	Protocol 020 [141]

[a] Description of the analysis population: see Appendix A
CI = confidence interval; ITT = intention-to-treat; PP = per-protocol.

2.3.1.2.3 External genital lesions

Both Goldstone et al. and Giuliano et al. reported on the VE against external genital lesions (EGL), which was defined as condylomata acuminata, penile, perianal or perineal intraepithelial lesions (PIN) (Table 2.3.16). No cases of penile, perianal or perineal cancer were found in either the vaccinated group or the control group during study follow-up [139, 140]. There were no differences reported in the observed efficacy between different sexual orientations.

Table 2.3.16 VE against external genital lesions (EGL) in males

Endpoint	Analysis population[a]	Age	Sexual orientation	Vaccine efficacy (95%CI)	Source
EGL any type	HPV naïve	16-26 yr.	Heterosexual ♂ and MSM	81.5 (58.0-93.0)	Protocol 020 [140]
	ITT	16-26 yr.	Heterosexual ♂ and MSM	59.3 (40.0-72.9)	Protocol 020 [140]
	PP	16-26 yr.	Heterosexual ♂ and MSM	83.8 (61.2-94.4)	Protocol 020 [139]
	ITT	16-26 yr.	Heterosexual ♂ and MSM	60.2 (40.8-73.8)	Protocol 020 [139]
EGL related to HPV6/11/16/18	HPV naïve	16-26 yr.	Heterosexual ♂ and MSM	90.8 (70.7-98.2)	Protocol 020 [140]
	ITT	16-26 yr.	Heterosexual ♂ and MSM	66.7 (48.0-79.3) *	Protocol 020 [140]
	PP	16-26 yr.	Heterosexual ♂ and MSM	90.4 (69.2-98.1)	Protocol 020 [139]
	ITT	16-26 yr.	Heterosexual ♂ and MSM	65.5 (45.8-78.6) *	Protocol 020 [139]
	PP	16-23 yr.	Heterosexual ♂	92.4 (69.6-99.1)	Protocol 020 [139]
	ITT	16-23 yr.	Heterosexual ♂	63.7 (39.3-79.1)	Protocol 020 [139]
	PP	16-26 yr.	MSM	79.0 (-87.9-99.6)	Protocol 020 [139]
	ITT	16-26 yr.	MSM	70.2 (23.0-90.2)	Protocol 020 [139]
EGL related to HPV31/33/35/39/45/51/52/56/58/59	HPV naïve	16-26 yr.	Heterosexual ♂ and MSM	67.1 (-83.9-6.8)	Protocol 020 [140]
	ITT	16-26 yr.	Heterosexual ♂ and MSM	50.3 (-16.5-80.3)	Protocol 020 [140]

[a] Description of the analysis population: see Appendix A
* Reasons for this slight difference in VE could not be found in the literature.
CI = confidence interval; EGL = external genital lesions; ITT = intention-to-treat; PP = per-protocol.

The VE against different grades of PIN was also estimated. The efficacy against EGL, independent of HPV type, is shown in Table 2.3.17. For the per protocol analysis populations, the VE against PIN of any grade was 100%, but the confidence interval was very broad and included zero [139, 140]. Besides that, Goldstone et al. reported a insignificant efficacy specifically against vaccine types HPV6/11/16/18 of 100% for both PIN1+ and PIN2+/3+ (respective 95% CIs -138.8-100% and -425.5-100%) [140].

Table 2.3.17 VE against different grades of PIN, independent of HPV type, among males (16-26 years of age)

Endpoint	Analysis population[a]	Vaccine efficacy (95%CI)	Source
PIN1 any type	PP	100 (-431.1-100)	Protocol 020 [139]
	ITT	25.6 (-393.8-69.7)	Protocol 020 [139]
PIN1+ any type	HPV naïve	50.7 (-224.3-95.5)	Protocol 020 [140]
PIN1+ HPV6/11/16/18	HPV naïve	100 (-138.8-100)	Protocol 020 [140]
PIN2/3 any type	PP	100 (-3,788.2-100)	Protocol 020 [139]
	ITT	-48.9 (-1,682.6-82.9)	Protocol 020 [139]
PIN2/3+ any type	HPV naïve	100 (-425.5-100)	Protocol 020 [140]
PIN2/3+ HPV6/11/16/18	HPV naïve	100 (-425.5-100)	Protocol 020 [140]

[a] Description of the analysis population: see Appendix A
CI = confidence interval; ITT = intention-to-treat; PIN = perineal intraepithelial lesions; PP = per-protocol.

Giuliano et al. reported on HPV DNA detection and persistent external anogenital infections based on specimens from the penis, scrotum, and perineal and perianal regions. Estimates were based on the ITT population. The VE against one-time HPV DNA detection of HPV6/11/16/18 overall was 27.1% (95% CI 16.6-36.3%). For heterosexual males and MSM, the VE were 31.3% (95% CI 19.4-41.5%) and 16.1% (95% CI -8.5-35.2%), respectively. Overall, the VE against persistent (same HPV type detected in anogenital swab or biopsy specimen collected on two or more consecutive visits with at least six months (±1) apart) anogenital infections with HPV types 6/11/16/18 was 47.8% (95% CI 36.0-57.6%). The respective VEs were 50.4% (95% CI 36.2-61.6%) and 43.6% (95% CI 19.5-60.8%) when stratified for heterosexual males and MSM, respectively [139].

2.3.2 Cross protection

In the Summary of Product Characteristics (SPC) as published by EMA [138], the vaccine efficacy for non-vaccine oncogenic HPV types is reported based on the PATRICIA trial (HPV-008; women 15-25 years) according to protocol (ATP). For the bivalent vaccine, statistically significant type-specific cross-protection is mentioned for HPV31 (6 months of persistent cervical infection 76.8% (95% CI 69.0-82.9%) and CIN2+ 87.5% (95% CI 68.3-96.1%)), HPV33 (6 months of persistent infection 44.8% (95% CI 24.6-59.9%) and CIN2+ 68.3% (95% CI 39.7-84.4%)), HPV45 (6 months of persistent infection 73.6% (95% CI 58.1%-83.9%) and CIN2+ 81.9% (95% CI 17.0-98.1%)) and HPV51 (6

months of persistent infection 16.6% (95% CI 3.6-27.9%) and CIN2+ 54.4% (95% CI 22.0-74.2%)).
For other hrHPV types, no statistically significant vaccine efficacies for the bivalent vaccine were reported in the SPC [138] for 6 months of persistent infection and CIN2+. For the quadrivalent vaccine, only statistically significant cross-protective vaccine efficacy was reported for HPV31 (CIN2+ 55.6% (95% CI 26.2-74.1%) [116].
RIVM estimated [142] the health gain in women, comparing the three available vaccines (bivalent, quadrivalent and nonavalent vaccines), and concluded that the bivalent was estimated to have about 10% more health gain than the quadrivalent vaccine as a result of the broader cross-protection reported in the EPAR documents. The approximate 10% difference was found when taking into consideration cervical cancer only, as well as when all HPV-related cancers in females were considered. Furthermore, the estimated health gain for the more recent nonavalent vaccine was estimated to be around 10% higher than for the bivalent vaccine [142].
Malagon et al. [143] performed a systematic review and meta-analysis on the cross-protective efficacy of the bivalent and quadrivalent vaccines. The results were based on three clinical trials for the bivalent vaccine (PATRICIA/HPV-008, HPV-007 and HPV-023) and on two trials for the quadrivalent vaccine (FUTURE I/II). FUTURE I/II data were merged in all publications, implying that heterogeneity could not be assessed.
For the three trials of the bivalent vaccine, heterogeneity was found for vaccine efficacy against 6 months of persistent infection with HPV31 and -45, and for HPV33 for CIN2+. In Table 2.3.18, the vaccine efficacy against persistent infection and CIN2+ for high-risk hrHPV type are reported for different trials. Estimates of efficacy tended to decline during follow-up, with the highest efficacy reported in the PATRICIA trial with shortest follow-up (mean 3.7 years; up to 4 years) compared with those with longer follow-up (HPV-007, mean 5.9 years, up to 6.4 years and HPV-023; up to 9 years). Malagon et al. concluded that the bivalent vaccine might offer greater cross-protection than the quadrivalent vaccine would, though this efficacy seemed to decline with time, possibly due to waning effects. At the population level, limited effects are to be expected if the duration of cross-protection is relatively short (e.g. 5 to 10 years). Furthermore, the differences between the two vaccines might partly be attributable to differences in trial design.
In a review of the bivalent HPV vaccine trials, Skinner et al. [121] reported that, in addition to the 4-year follow-up results of the Costa Rica trial in 18 to 25-year-old women (while no baseline evidence of infection was known for the HPV type under analysis), there were statistically significant vaccine efficacies against six months of persistent infection for HPV31 (64.7% (42.6-78.9)) and HPV45 (73.0 (45.3-87.8)) and HPV31/33/45 (60.0 (43.1-72.7)). But for CIN2+, no statistical significant efficacies were reported.
Skinner et al. [121] also reported the results of the VIVIANE study (four years follow-up, women > 25 years) among women with no baseline evidence for infection with the HPV-type under analysis. Here, statistically significant vaccine efficacies against six months of persistent infection were also reported for HPV31 (79.1% (27.6-95.9) and HPV45 (76.9 (18.5-95.6)).

Szarewski et al. [144] performed a post-hoc analysis of the PATRICIA trial to estimate the vaccine efficacy of the bivalent vaccine against low-risk HPV types 6 and 11 and found in the total vaccinated cohort, naïve for all types at baseline, a vaccine efficacy of 34.5% against six months of persistent infection (34.5% (11.3-51.8) for HPV6/11). For HPV6, HPV53 and HPV74, statistically significant efficacies of 34.9% (9.1-53.7), 26.7 (8.1-41.7) and 49.5% 31-68.3) were reported. They speculated that cross-reactivity at the T helper cell level is a plausible mechanism for the vaccine-induced cross-protection that was observed. They concluded that the clinical significance of this post-hoc analysis remained unclear.
Kreimer et al. also explored the VE of the bivalent vaccine against anal HPV infections related to HPV31/33/45. For the full cohort, the VE was 49.4% (30.3-63.6%) and in the restricted cohort (HPV naïve and completely vaccinated), the VE was 61.8% (42.8-75.0%) [132].
Herrero et al. also estimated the VE for oral prevalent infections against other oncogenic types four years after vaccination with the bivalent vaccine. There was no evidence of statistically significant protection against HPV31/39/51/52/56/39. The overall VE against oncogenic types combined was 45.7% (95%CI 6.9-69.0%), excluding HPV16/18, which was estimated at 13.2% (95%CI -61.1-53.6%) [145].

Scherpenisse et al. studied the inhibition of HPV antibodies present in sera from vaccinated girls with VLP16 and VLP18. After vaccination, cross-reactive antibodies were mainly species-specific. A significant reduction in antibody levels of phylogenetically related HPV types was observed. VLP16 inhibition was between 76% and 88% for HPV31, 33, 52 and 58. Also, some inhibition was found for HPV45 (28%). For VLP18, the inhibition was also mainly species-specific (alpha 9); HPV45 inhibition was 73%.
This study also showed a three times higher avidity index of vaccine-induced antibodies compared with naturally induced antibodies [146].

Table 2.3.18 HPV-efficacy against persistent cervical infection (>= 6 months) and CIN2+ with individual non-vaccine type HPV as reported by Malagon et al. in HPV-naïve population [143]

		Persistent cervical infection			CIN2+		
		Vaccine (cases/ participants)	Control (cases/ participants)	Vaccine efficacy % (95% CI)	Vaccine (cases/ participants)	Control (cases/ participants)	Vaccine efficacy % (95% CI)
HPV31							
FUTURE I/II	quadrivalent	31/1,036	57/1,032	46.2% (15.3-66.4)	8/4,616	27/4,680	70.0% (32.1-88.2)
PATRICIA	bivalent	38/5,427	163/5,399	77.1% (67.2-84.4)	3/5,466	28/5,452	89.4% (65.5-97.9)
HPV-007	bivalent	5/455	9/430	47.7% (-73.8-86.2)	0/528	0/516	NA
HPV-023	bivalent	6/226	6/201	10.3% (-235.6-76.0)	0/249	1/237	100% (-3,598-100)
HPV33							
FUTURE I/II	quadrivalent	15/1,036	21/1,032	28.7% (-45.1-65.8)	12/4,616	16/4,680	24.0% (-71.2-67.2)
PATRICIA	bivalent	53/5,427	92/5,399	43.1% (19.3-60.2)	5/5,466	28/5,452	82.3% (53.4-94.7)
HPV-007	bivalent	6/458	5/436	-15.5% (-378.4-70.6)	2/529	1/519	-95.6% (-11,437.7-89.8)
HPV-023	bivalent	6/226	4/204	-37.1% (-560.4-67.5)	2/251	1/238	-90.4% (-11,130.2-90.1)
HPV45							
FUTURE I/II	quadrivalent	24/1,036	26/1,032	7.8% (-67.0-49.3)	3/4,616	2/4,680	-51.9% (-1,717.8-82.6)
PATRICIA	bivalent	13/5,427	612/5,399	79.0 (61.3-89.4)	0/5,466	8/5,452	100 (41.7-100)
HPV-007	bivalent	2/460	4/438	52.1% (-233.9-95.7)	0/528	0/518	NA
HPV-023	bivalent	5/226	3/205	-52.7% (-883.5-70.3)	0/249	0/236	NA

		Persistent cervical infection			CIN2+		
		Vaccine (cases/ participants)	Control (cases/ participants)	Vaccine efficacy % (95% CI)	Vaccine (cases/ participants)	Control (cases/ participants)	Vaccine efficacy % (95% CI)
HPV52							
FUTURE I/II	quadrivalent	50/1,036	61/1,032	18.4% (-20.6-45.0)	17/4,616	23/4,680	25.2% (-46.4-62.5)
PATRICIA	bivalent	231/5,427	281/5,399	18.9% (3.2-32.2)	14/5,466	20/5,452	30.4% (-45.0-67.5)
HPV-007	bivalent	22/453	19/424	-8.2% (-111.4-44.1)	1/524	4/515	75.7% (-145-99.5)
HPV-023	bivalent	23/223	21/197	3.7% (-82.9-49.1)	1/247	3/237	68.3% (-295.4-99.4)
HPV58							
FUTURE I/II	quadrivalent	35/1,036	37/1,032	5.5% (-54.3-42.2)	16/4,616	20/4,680	18.9% (-64.7-60.7)
PATRICIA	bivalent	93/5,427	87/5,399	-6.2% (-44.0-21.6)	9/5,466	14/5,452	36.1 (-58.6-75.6)
HPV-007	bivalent	7/458	7/435	4.3% (-219.8-71.3)	0/529	1/517	100 (-3,679.0-100)
HPV-023	bivalent	12/224	10/204	-10.4% (-185.2-56.3)	0/250	3/237	100 (-128.6-100)

CI = confidence interval; CIN = cervical intraepithelial neoplasia.

2.3.3 Immunogenicity

As described in Section “2.1 Availability of vaccines”, immunogenicity data was used to bridge (immunobridging) clinical vaccine efficacy (which was shown in individuals older than 15) to (other) age groups, genders and reduced dose schedules. Immunogenicity can be defined as the ability of any particular epitope to provoke an immune response in the body, either via the formation of antibodies or cell mediated immunity (CMI) [147].

The 2vHPV, 4vHPV and 9vHPV vaccines were initially licensed in a three-dose schedule (0/1/6 months or 0/2/6 months) for recipients from the age of 9. In 2014, the 2vHPV and 4vHPV vaccines were licensed in a reduced two-dose schedule for individuals between the age of 9 and, respectively, 15 and 14.[116, 138] The 9vHPV vaccine was approved for a two-dose schedule for girls and boys aged 9-14 by the European Commission in April 2016 [117]. But up to now, there has been no serologic correlate of immunity or a determined minimal level of protection.

2.3.3.1 Immunogenicity in female adolescents/adults (older than 15)

2.3.3.1.1 Bivalent vaccine

In females (ages 15-25), the 2vHPV vaccine continues to give high and sustained antibody levels, 10.8-fold and 10.0-fold higher than after natural infection for HPV16 and HPV18 respectively, up to 9 years after the administration of the vaccine [138, 148].

2.3.3.1.2 Quadrivalent vaccine

The 4vHPV vaccine showed sustained high antibody responses up to 9 years after administration of the vaccine in women (16-23 years) [149].

2.3.3.1.3 Nonavalent vaccine

The antibody response has been shown to persist at least 3.5 years after vaccination, the antibody titres being non-inferior for HPV6/11/16/18 compared with the 4vHPV vaccine (non-inferiority margin: lower boundary for GMT ratio (nonavalent/quadrivalent vaccine) > 0.67). Depending on the HPV type, 78-98% of the women remained seropositive [117].

2.3.3.1.4 Comparison between vaccines

In women (ages 18-45) who received vaccination according to the three-dose schedule, the 2vHPV vaccine induced higher serum antibody responses than the 4vHPV vaccine. Differences in the geometric mean titre of neutralizing antibodies against HPV16 were 2.3-7.8 fold, between the 2vHPV and 4vHPV-vaccines, five years after vaccination, depending on the age of the vaccine administration. Antibody responses against HPV 18 after five years differed 7.8-13.0 fold between the two vaccines [150].

2.3.3.2 Immunogenicity in young female adolescents (below 16 years)

2.3.3.2.1 Three-dose schedule

2.3.3.2.1.1 Bivalent vaccine

A long-term follow-up showed that the 2vHPV vaccine administered to preadolescent girls was immunogenic for up to 9 years after a three-

dose schedule. The induced antibody responses against HPV16/18 were predicted, by both piecewise and modified power-law models, to persist for at least 20 years before reaching natural infection antibody levels [138, 151].

2.3.3.2.1.2 Quadrivalent vaccine

Most girls and boys 9-15 years of age that have received the 4vHPV vaccine remained seropositive for up to 10 years after vaccination. Depending on the type of HPV, 60-96% and 78-98% were seropositive (measured by the cLIA and IgG LIA respectively)b [116]. Comparing the 4vHPV in a three-dose schedule between women (ages 16-23) and girls and boys (ages 10-15), GMTs in younger girls and boys were non-inferior to the females with titres, and were even 1.7 to 2.7 fold higher than that of the 16 to 23-year-old females [152].

2.3.3.2.1.3 Nonavalent vaccine

The recently developed nonavalent (9vHPV) vaccine elicited similar antibody responses (GMTs) as those elicited by the 4vHPV vaccine for HPV6/11/16/18 in girls aged 9-15 years old. Additionally, all participants seroconverted for the HPV types 31/33/45/52/58 [153]. After a third dose of 9vHPV, 98% of young women between the age of 12 and 16 that had previously received the 4vHPV-vaccine sero-converted for the additional HPV vaccine types 31/33/45/52/58. The antibody concentrations, however, were lower (1.6-2.9 fold depending on HPV type) than they were in females that had not previously received the 4vHPV vaccine. Data can be found in Table 5 of the original manuscript [154].

2.3.3.2.2 Immunogenicity of the two-dose schedule

2.3.3.2.2.1 Bivalent vaccine

Girls ages 9 to 14 that received a two-dose schedule (0,6 months) had all seroconverted to HPV types 16 and 18 one month after the second dose. The induced immune response after the 2 doses was non-inferior (upper boundary 95% CI for GMT ratio 3-/2-doses < 2.0) to the response obtained after three-doses in females aged 15 to 25 years [138, 155, 156]. A follow-up study showed immunogenicity up to 60 months after vaccination. Antibody levels at time point of 60 months were comparable to antibody responses elicited by the three-dose schedule [157]. Using the non-inferiority margin of 2.0, the 2-dose schedule in preadolescent girls was non-inferior to the 3-dose schedule in young women up to 60 months after the first vaccination for the 2vHPV vaccine (Figure 2.3.2).

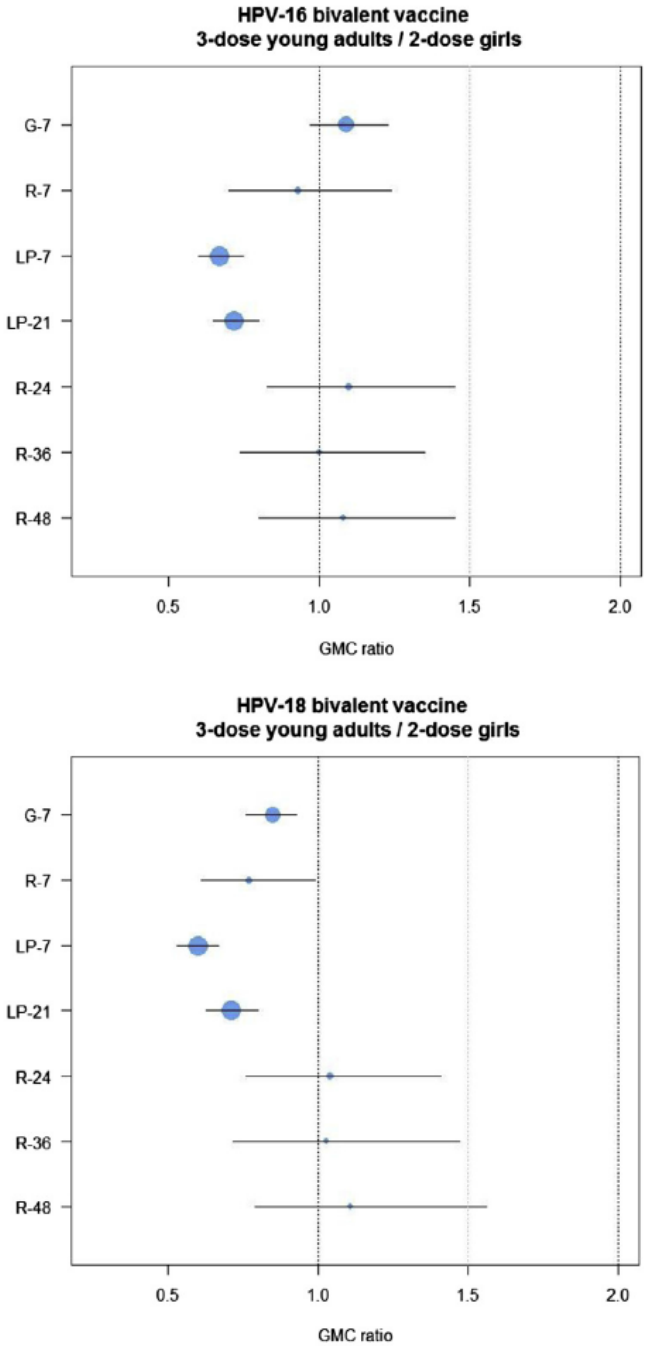

Figure 2.3.2 GMC ratios for the bivalent vaccine. GMC after a three-dose (0,1/2, 6 months) schedule in young adults (15-25 yrs) divided by a two-dose schedule (0,6 months) in preadolescents (9-15 yrs) in the according-to–protocol population (principle of immunobridging). The initial mentioned is the first letter of last name of the author (R=Romanowski [155, 156]l, LP=Lazcano-Ponce [158], G=GSK study HPV-070 [138]), the number is the number of months after the first dose. The dashed line at 2.0 illustrates the non-inferiority margin; if the upper boundary of the confidence interval exceeds this boundary, non-inferiority could not be concluded.
From: Donken et al. 2015 [159]
GMC = geometric mean concentration.

In contrast, in a cross-sectional study conducted among Dutch girls (HPV2D), the GMCs for HPV16/18 of the 2vHPV vaccine were not found to be non-inferior for the two-dose schedule compared with the three-dose schedule, with the exception of HPV18 at 2-3 years post-vaccination [84, 160]. In a meta-analysis published in 2015, non-inferiority for HPV16 could not be concluded at two years after the first dose [159].

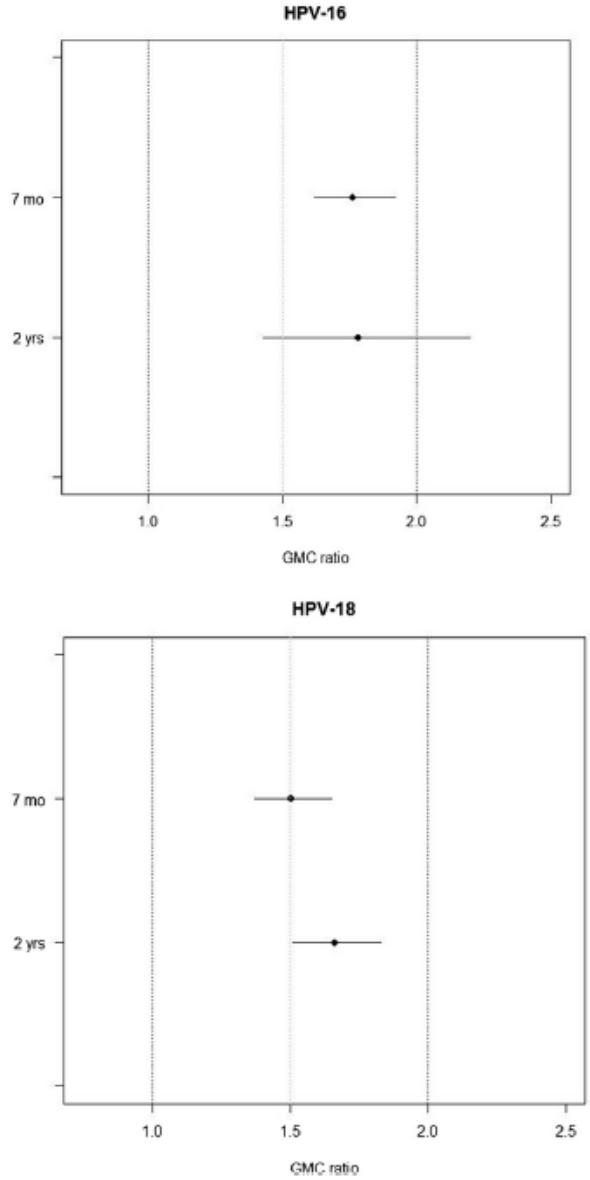

Figure 2.3.3 Pooled estimates for the GMC ratio for a three-dose (0, 1/2, 6 months) schedule divided by a two-dose (0, 6 months) schedule of the bivalent vaccine in girls. Two studies were included for this meta-analysis, Romanowski et al., 2011 [156] and Lazcano-Ponce et al., 2014 [158]. Shown in grey are the GMC ratios on which the pooled estimates are based; shown in bold are the pooled estimates.
From: Donken et al. 2015 [159]
GMC = geometric mean concentration.

2.3.3.2.2.2 Quadrivalent vaccine

A two-dose (0,6 months) schedule was non-inferior in 9 to 13-year-olds to the three-dose in 16 to 27-year-olds up to 36 months of follow-up in [161] (Figure 2.3.4). No significant differences in GMT measured with IgG LIA were present at 60 months when comparing the two-dose with the three-dose schedule among girls 9-13 years of age [162]. Using the cLIA assay for up to 36 months, no significant differences were found for HPV16 and, for HPV18, the GMT of the two-dose group was lower than for the three-dose group [163].

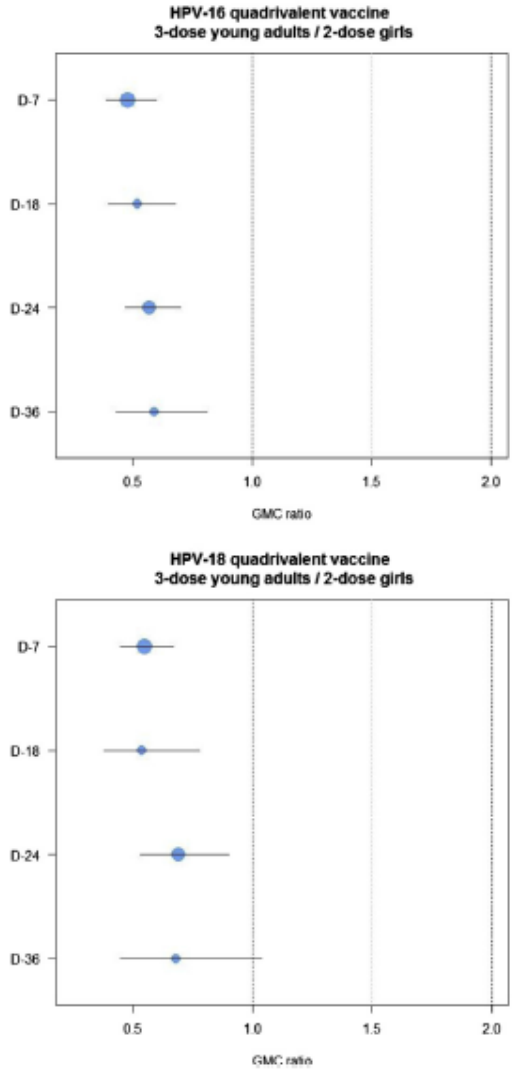

Figure 2.3.4 GMC ratios for the quadrivalent vaccine. GMC after a three-dose (0,1/2, 6 months) schedule in young adults (15-25 yrs) divided by a two-dose schedule (0,6 months) in preadolescents (9-15 yrs) in the according-to–protocol population (principle of immunobridging). The initial mentioned is the first letter of last name of the author (D=Dobson [161]), the number is the number of months after the first dose. The dashed line at 2.0 illustrates the non-inferiority margin; if the upper boundary of the confidence interval exceeds this boundary, non-inferiority could not be concluded.
From Donken et al. 2015 [159]
GMC = geometric mean concentration.

2.3.3.2.2.3 Nonavalent vaccine

Girls and boys aged 9 to 14 years that received a two-dose schedule of the 9vHPV vaccine showed non-inferior antibody levels, using a margin of 0.67 in this study for the ratio of the antibody GMT, when compared to a three-dose schedule (adolescent and young girls aged 16-26 years) at 4 weeks post-vaccination [164].

2.3.3.2.2.4 Head to head comparison of vaccines

A head-to-head comparison study showed that the antibody concentrations were higher after administration of the 2vHPV vaccine when compared with the 4vHPV vaccine, both administered in a two-dose schedule [150, 165].

Using a non-inferiority margin of 2.0, the 2-dose schedule in preadolescent girls showed non-inferior antibody levels compared with the 3-dose schedule in young women, up to 60 months for the 2vHPV vaccine and up to 36 months for the 4vHPV vaccine after the first dose for HPV16/18 [155-158, 161, 165]). An exception was the study of Krajden et al, in which non-inferiority could not be concluded for HPV18 at 24 and 36 months in girls vaccinated with the 4vHPV (two-dose (9-13 years) vs. three-dose (16-23 years). However, it should be mentioned that the confidence intervals for the GMC ratios were very wide, although the point estimates were below one (both 0.74) [163, 166].

2.3.3.2.3 Immunogenicity after one dose HPV

Some studies indicate that it would be worthwhile to perform future trials on HPV vaccines using a single-dose arm to assess the efficacy of a further reduced dose schedule [167-169]. Sankaranarayanan et al. reported that, after one dose of quadrivalent vaccine in girls, lower antibody concentrations were found than were present with a 2- or 3-dose schedule. However, titres were stable for up to 36 months and the mean avidity index of one-dose recipients was non-inferior to that measured after three doses [168]. With a limited number of participants receiving one HPV dose of quadrivalent vaccine in another study, immune memory and antibody persistence was shown for up to six years. These girls had been vaccinated 6 years earlier and showed an amnestic antibody response one month after vaccination with the bivalent vaccine. The response was similar to girls who received two or three doses [169]. Safaeian et al. reported that, after one HPV dose with bivalent vaccine, lower antibody levels were found than were found after two doses, but that antibody titres were stable from 6 months to 48 months [167].

2.3.3.3 Immunogenicity in Males

2.3.3.3.1 Bivalent vaccine

Immunogenicity in males aged 10 to 18 years after receiving the 2vHPV vaccine was assessed in two clinical trials (HPV-011 (N=173) and HPV-040 (N=556)). The data showed comparable immunogenicity in males and females. In study HPV-011, all subjects seroconverted to both HPV16 and -18 and GMT levels were non-inferior to those observed in females aged 15 to 25 years in study HPV-012 [138].

2.3.3.3.2 Quadrivalent vaccine

The antibody concentrations following the 4vHPV vaccination in adult men (ages 27-45) was comparable to those observed in younger men [170]. Hillman et al. showed that antibody GMTs against HPV6/11/16 and 18 among heterosexual men (16-23y) and MSM (16-26y) were 448 mMU/mL, 624 mMU/ml, 2404 mMU/ml and 402 mMU/ml, respectively. These results were lower than those obtained for females 16 to 23 years of age (549 mMU/mL, 635 mMU/ml, 3870 mMU/ml and 741 mMU/ml). Despite this, the vaccine still proved to be highly immunogenic for all vaccine types [171]. Also, in saliva collected (from males ages 27-45), antibodies against HPV16 and -18 induced by the 4vHPV vaccine could be found. The antibody concentrations were around 3 logs lower than the antibody concentration measured in sera, but correlated significantly with the serum levels [172].

2.3.3.3.3 Nonavalent vaccine

Castellsague et al. studied the immunogenicity of the 9vHPV vaccine in men between 16 and 26 years of age compared with women of the same age. At the time point of 7 months, the geometric antibody concentrations for the nine vaccine types in heterosexual men were non-inferior (lower boundary 95% CI for GMT ratio men divided by women >0.67) to those in women. For all 9vHPV vaccine types, antibody responses in MSM were two-fold lower than they were in heterosexual men [173]. Van Damme et al. observed that antibody responses against HPV6/11/16 and 18 elicited by the 9vHPV vaccine, after a three-dose schedule, were similar to 4vHPV vaccine antibody responses in men [174].

2.3.3.4 Immunogenicity in immunocompromised individuals

In female juvenile idiopathic arthritis (JIA) patients, the 2vHPV vaccine was immunogenic and well-tolerated, similar to results in healthy females. HPV-specific antibodies and B-cell responses, however, were lower in patients than they were in the healthy control females [175]. Female patients with rheumatic diseases, particularly those with systemic lupus erythematosus (SLE), showed reduced concentrations of antibodies against HPV16 and -18 after three vaccine doses, compared with healthy age-matched girls, albeit that this difference did not reach a significant level. One Juvenile Dermatomyositis (JMD) patient did not mount an HPV 18 antibody response and remained seronegative at the time point of 7 months. Over 96% of HIV-infected subjects aged 7- 12 years that received the 4vHPV vaccine seroconverted to all four antigen types. The GMTs were lower than those found in non-HIV infected subjects of the same age [116, 176]. In HIV-infected women (13-45 years of age) vaccinated with the 4vHPV vaccine, the vaccine was considered immunogenic. However, women with a high HIV RNA load (>10.000 copies/mL) and/or a low CD4 count (<200 cells/ µL) showed lower seroconversion rates [177]. Moreover, HIV-infected women with a suppressed HIV viral load at the time of 4vHPV vaccination (three-dose schedule) showed higher antibody responses than did HIV-infected women with a non-suppressed viral load [178].

2.3.3.5 Avidity of the antibody response induced after vaccination

The strength whereby an antibody binds to an antigen via a single binding is called affinity. The higher this affinity for an antigen, the lower

the number of antibodies needed for neutralization of the antigen. The accumulated strength of multiple affinities is called avidity and could be of importance for protection after vaccination [146].

2.3.3.5.1 Bivalent vaccine

In the HAVANA cohort study conducted among Dutch vaccinated (three-doses) and unvaccinated girls that were eligible for the catch-up vaccination campaign, Scherpenisse et al. explored the avidity. Avidity of vaccine-derived HPV-specific antibodies was three times higher than that of antibodies induced by HPV infection.[146] No difference between antibody avidity levels was seen after a two-dose 2vHPV schedule (girls 9-14y, 0, 6 months) compared with a 3-dose schedule (young women 15-25y) up to 48 months [179]. GMCs for HPV16 and 18 after a two-dose schedule did not meet the non-inferiority criteria in comparison with a three-dose schedule, as in the Dutch HPV2D study previously described. In contrast, the geometric mean antibody avidity index for vaccine types did show non-inferiority for the two-dose schedule (0, 6 months) compared with the three-dose schedule after two years. This indicates a similar quality of the immune response [84, 160].

2.3.3.5.2 Quadrivalent vaccine

For the 4vHPV vaccine as well, the geometric mean (GM) avidity index after a two-dose schedule (girls 10-18 years) was non-inferior to that after a three-dose schedule (girls 10-18 years) for up to 18 months for all vaccination groups [168].

2.3.3.6 Cellular immunity after HPV vaccination

For long-term vaccine-induced protection and efficacy, cellular immunity is thought to be crucial [180]. For clearance of an infection, T-effector cells are involved, whereas memory T cells enable B cells to provide a faster and stronger immune response. Memory B cells can subsequently differentiate into long-lived plasma cells, which secrete pathogen-specific antibodies [64]. A study was conducted in which a comparison was made between two-dose schedule girls (9-13y) and a three-dose schedule in young women (16-26y) for the bivalent and quadrivalent vaccines. In this study concerning 4vHPV, comparable memory B-cell frequencies for HPV6/11/16/18 were found. However, lower memory T-cell formation for HPV6/16/18 was observed in the two-dose schedule, though memory T-cell formation against HPV11 was comparable between the two groups [181].

A study conducted among girls (9-14 years) vaccinated with the 2vHPV (two-dose) or 4vHPV vaccine (two-dose or three-dose) showed a large overlap in the range of cell-mediated immune responses between the three groups. For instance, higher numbers of B and CD4+ cells in the 2vHPV (two-dose) vaccinated group were found when compared with the 4vHPV vaccine group (both 2-dose and 3-dose) [165]. Moreover, women between the ages of 18 and 45 years that received a three-dose schedule of the 2vHPV vaccine showed higher HPV-18-specific memory B-cell responses for up to 24 months, compared with those vaccinated with the 4vHPV vaccine. While in the seventh month after the primary vaccination a similar proportion of circulating memory B-cells specific for HPV16 were found in responders of both groups, the geometric mean of circulating memory B cells was higher in the women vaccinated with the

2vHPV vaccine, compared with the women vaccinated with the 4vHPV vaccine. In addition, the number of CD4+ T cells was higher in the 2vHPV vaccine recipients than in the 4vHPV vaccine recipients for up to 24 months [182].

2.3.4 Vaccine effectiveness

2.3.4.1 Impact and vaccine effectiveness in various countries

Since 2007, several countries around the world have implemented HPV vaccination in their NIPs. Various countries have studied the impact and vaccine effectiveness of the bivalent and quadrivalent HPV vaccines after its introduction.

2.3.4.1.1 HPV infections

In a review of 20 studies among females in high-income countries, the HPV prevalence of the HPV-related endpoints HPV infection, anogenital warts and high-grade cervical lesions were compared between pre-vaccination periods and post-vaccination periods (Table 2.3.19) [183]. The reduction in the overall prevalence of HPV16/18 was 64% in 13 to 19-year-olds and 31% in 20 to 24-year-olds and was associated with vaccination coverage (coverage ranged between 34% and 89%; p=0.005).

Table 2.3.19 Population-level impact following HPV-vaccination programmes in high-income countries [183]

Endpoint (HPV infection, anogenital warts, high-grade cervical lesions)	Population	RR* (95% CI)
HPV16/18	13-19 year-old girls	0.36 (0.25-0.53)
	20-24 year-old women	0.69 (0.47-1.01)
HPV31/33/45	13-19 year-old girls	0.72 (0.54-0.96)
	20-24 year-old women	0.93 (0.70-1.23)
HPV31/33/45/52/58	13-19 year-old girls	0.94 (0.79-1.13)
	20-24 year-old women	0.96 (0.86-1.08)
hrHPV types (except 16/18)	13-19 year-old girls	1.04 (0.87-1.25)
	20-24 year-old women	1.09 (0.98-1.22)

* RR for the post-vaccination period compared to the pre-vaccination period.
CI = confidence interval; hr = high-risk; RR = relative risk.

In a review of the effectiveness of the quadrivalent vaccine on cervical/vaginal HPV infection and disease, declines in prevalent vaccine types were seen within 4 years after vaccine availability, irrespective of study design and vaccination coverage. In Australia (83% coverage of >=1 dose) and the United States (57% coverage >=1 dose), reductions of 76-89% were seen in prevalent HPV6/11/16/18 cervical/vaginal infections in vaccinated versus unvaccinated females within 6 years of HPV vaccination. In these countries, reductions in infection prevalence (34-82%) were also seen in the vaccinated females versus the pre-vaccine era, even in unvaccinated women in the vaccine era versus the pre-vaccine era (17-49%), possibly due to herd protection [184].

In England, among women visiting clinics for chlamydia screening, with an estimated vaccination coverage of 67%, the vulvar/vaginal prevalence of HPV16/18 declined from 17.6% (95% CI 15.3-19.9%) in

the pre-vaccination period to 4.0% (95% CI 2.8-5.1%) four to five years after vaccination in 16 to 18-year-olds (adjusted OR 0.5; 95% CI 0.3-1.3) and from 16.9% (95% CI 14.3-19.5%) to 8.7% (95% CI 7.2-10.2%) in 19 to 21-year-olds (adjusted OR 1.2; 95% CI 0.6-4.5). The prevalence of HPV31/33/45 declined only in the youngest age group, from 8.4% (95% CI 6.7-10.1) to 5.8% (95% CI 4.4-7.2%) (adjusted OR 0.9; 95% CI 0.5-1.5) [185].

The vaccine effectiveness of one, two and three doses of the bivalent vaccine in women who attended for their first cervical smear in Scotland was 48.2% (95% CI 16.8-68.9), 54.8% (95% CI 30.7-70.8) and 72.8% (95% CI 62.8-80.3), respectively, for prevalent HPV16 and/or HPV18 infection and -1.62% (95% CI -85.1-45.3), 48.3% (95% CI 7.6-71.8) and 55.2% (95% CI 32.6-70.2), respectively, for prevalent HPV31, HPV33 and HPV45 infection [186].

2.3.4.1.2 Genital warts

In a meta-analysis of high-income countries using the quadrivalent vaccine, the RR for anogenital warts in the post-vaccination period compared with the pre-vaccination period was 0.69 (95% CI 0.60-0.79) for 15 to 19-year-old girls and 0.89 (95% CI 0.79-2.01) for 20 to 39-year-old girls [183]. In boys and men, no significant reduction was found following female-only vaccination, i.e. RR 0.95 (95% CI 0.84-1.08) for 15 to 19-year-old boys and 1.01 (95% CI 0.88-1.17) for 20 to 39-year-old men [183]. However, in countries with high female vaccination coverage, anogenital warts were reduced significantly in women aged 20–39 years (RR 0·68; 95% CI 0·51–0·89) and in boys aged 15–19 years (RR 0·66; 95% CI 0·47–0·91).

A study in Denmark among women showed a significant decrease in the risk of genital warts with each dose of quadrivalent HPV vaccine (IRR_{1vs0} 0.51; 95% CI 0.46-0.56, IRR_{2vs1} 0.44; 95% CI 0.37-0.51, IRR_{3vs2} 0.46; 95% CI 0.39-0.54). For two-dose recipients, the incidence of genital warts was reduced by extension of the interval from two months to four, five and six months (i.e. by 45%; 95% CI 20-62%, 55%; 95% CI 35-69%, and 63%; 95% CI 44-75%, respectively) [187].

Declines in the prevalence and incidence of genital warts in women and men were seen especially in countries with high vaccination coverage with quadrivalent vaccine and particularly in the youngest age groups (reductions up to 92.6%) [184].

2.3.4.1.3 Cervical abnormalities

Declines in low-grade and high-grade cervical abnormalities were seen in vaccinated age-groups 12-26 years old, i.e. 19-47% and 36-48%, respectively, in low-grade and high-grade cervical abnormalities [184]. In a Swedish register-based cohort between 2006 and 2014, the largest declines for CIN2 and CIN3 were seen in girls who were <17 years of age at the first dose (75 and 84%), 46% for CIN2 and 57% for CIN3 in age group 17-19 years at the first dose, and 22% for CIN2 and 25% for CIN3 were seen in those aged 20-29 years at the first dose, respectively [188]. In another study conducted in Denmark, six years after licensure of the vaccine, declines in CIN2+ and CIN3+ were found – by 73% and 80%, respectively, for the youngest vaccinated birth cohort 1993/1994,

and down to 12% and 22% for CIN2+ and CIN3+ for the oldest vaccinated birth cohort 1989/1990 [184].

Crowe et al. studied the vaccine effectiveness for the prevention of cervical abnormalities four years after the implementation of quadrivalent HPV vaccination in Australia. Adjusted ORs of HPV-vaccine exposure were assessed among cases with high-grade cervical abnormality and cases with low-grade abnormality or abnormal cytology compared with the HPV-vaccine exposure among controls. ORs decreased with number of doses, i.e. for high-grade cases: 0.95 (95% CI 0.77-1.16), 0.79 (95% CI 0.64-0.98) and 0.54 (95% CI 0.43-0.67) for one, two and three doses, respectively, and for other cases: 0.95 (95% CI 0.89-1.02), 0.79 (95% CI 0.74-0.85), and 0.66 (95% CI 0.62-0.70), respectively, for one, two and three doses [189]. This leads to vaccine effectiveness estimates for three doses of 46% for high–grade disease and 34% for other cases. The authors conclude that the quadrivalent HPV vaccine conferred statistically significant protection against cervical abnormalities in young women who had not started screening before the implementation of the vaccination programme in Queensland, Australia.

2.3.4.2 Vaccine effectiveness in the Netherlands

In 2009, an ongoing prospective cohort study (HAVANA) was initiated among 14 to 16 year-old girls that were eligible for the catch-up vaccination campaign that started in 2009. The primary aim of this study is to monitor the effect on HPV type distribution amongst vaccinated and unvaccinated young women. Yearly participants are asked to hand in a vaginal self-swab, which is then tested for the presence of HPV DNA [50, 190]. High vaccine effectiveness is found against both incident and persistent infections up to five years post-vaccination for both vaccine types (HPV16/18) and including cross-protective types (HPV31/45). (Table 2.3.20) [84, 191]. The VE against persistent HPV16/18 infections was 100% and, including cross-protective types, 89% among adolescents naïve for these types before vaccination. Type-specific incidence and persistence rates for high-risk HPV types among both vaccinated and unvaccinated participants is shown in Figure 2.3.5. Significant differences in type-specific incidence rates between vaccinated and unvaccinated participants were found for HPV16, -18, -31 and -45 and for persistence for HPV16 and HPV18.

Table 2.3.20 Vaccine effectiveness (VE) up to five years post-vaccination as observed in the HAVANA-study

HPV types	Infections (n) / Person years at risk Vaccinated	Infections (n) / Person years at risk Unvaccinated	VE	95% CI	Adjusted * VE	95% CI
Incident infections						
HPV16/18	25/2,996	87/2,697	74%	(59-83%)	78%	(61-84%)
HPV16/18/31/45	37/3,000	147/2,686	77%	(67-84%)	77%	(66-84%)
Persistent infections						
HPV16/18 (#)	0/2,990	27/2,692	100%	##	100%	##
HPV16/18/31/45 (#)	5/2,990	39/2,685	88%	(71-95%)	89%	(74-96%)
HPV16/18	10/3,009	34/2,712	74%	(46-87%)	79%	(57-90%)
HPV16/18/31/45	15/3,009	46/2,712	71%	(57-90%)	76%	(56-87%)

#= Among participants negative at baseline, ##= model does not converge
* Adjusted for the following baseline characteristics: age, urbanization degree, education, ethnicity, ever smoked, currently smoking, contraception use, ever had sexual intercourse, age of partner, number of sexual partners during lifetime.
CI = confidence interval; VE = vaccine effectiveness.

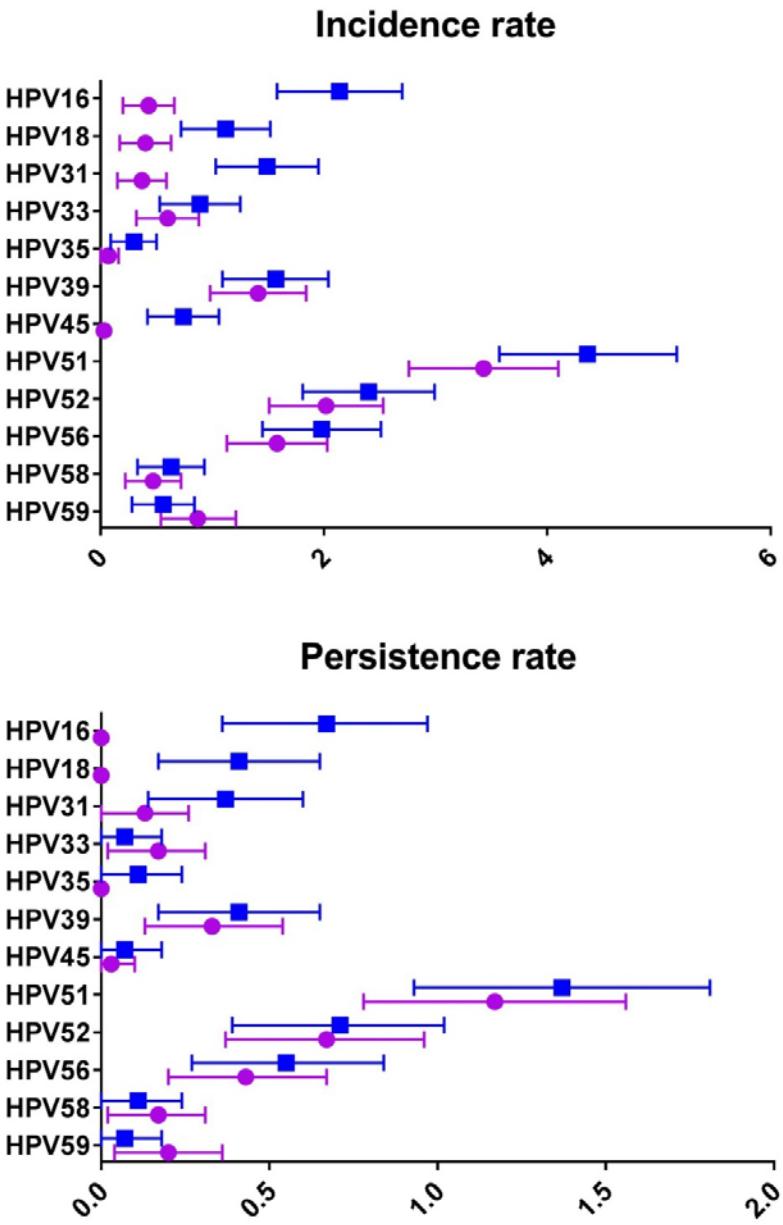

Figure 2.3.5 HR HPV-type-specific incidence (panel A) and persistence rates (panel B) up to five years post-vaccination as observed among vaccinated (purple) and unvaccinated (blue) participants of the HAVANA-study.

Vaccinated participants were completely vaccinated with the recommended schedule of three-doses (0, 1, 6 months) at that time.

Additionally, bivalent vaccine effectiveness against HPV types included in the nonavalent vaccine was studied. The adjusted overall VE up to five years after vaccination against incident HPV6/11/16/18/31/33/45/52/58 infections was 49% (95% CI 39-58%); for persistent infections this was 44% (21-59%).

To monitor possible changes in HPV dynamics over time, a biennial cross-sectional study among 16 to 24 year-old male and female STI clinic attendees (PASSYON) was set up [55]. In 2009 (n=1,696), 2011 (n=1,905), 2013 (n=1,990) and 2015 (n=1,977), this study took place in STI clinics throughout the Netherlands. The genital samples collected were analysed for type-specific HPV DNA. The percentage of participants that reported to be vaccinated has increased over the years; 2% in 2009, 5% in 2011, 13% in 2013 and 26% in 2015. The percentage of women testing positive for HPV16 and/or HPV18 decreased from 23% in 2009, before vaccination was implemented, to 15% in 2015 ($p<0.01$). Among heterosexual men, there was also a decreasing trend in the percentage testing positive for HPV16 and/or HPV18 (from 17% in 2009 to 11% in 2015, $p<0.01$), suggesting possible herd immunity from girls' vaccination. While the prevalence of HPV16 and HPV18 decreased over time, the percentage of women testing positive for another hrHPV type increased from 50% in 2009 to 58% in 2015 ($p<0.01$). This could partially be explained by increased sexual risk behaviour in the study population, further exploration is ongoing. Overall, the percentage of women and heterosexual men testing positive for an hrHPV type remained stable over time ($p=0.15$ and 0.93, respectively). Among MSM, there were no clear trends in HPV positivity [84].

The PASSYON-study was also used to calculate the VE against type-specific high-risk HPV positivity. Data from all vaccine-eligible women with a known self-reported vaccination status (cohorts born from 1993 onwards, n=1087) was used for this. Type-specific HPV positivity was compared between women that reported they had been vaccinated at least once and women that reported they were unvaccinated. Type-specific VE against all high-risk types are presented in Figure 2.3.6. The VE against HPV16/18 is high and in line with previous VE estimates from vaccine trials. In addition, significant cross-protection from the bivalent vaccine against HPV45, -35, -31 and -52 was found [192] . A negative VE for HPV59 was observed, interpretation of this finding is at this point unsure.

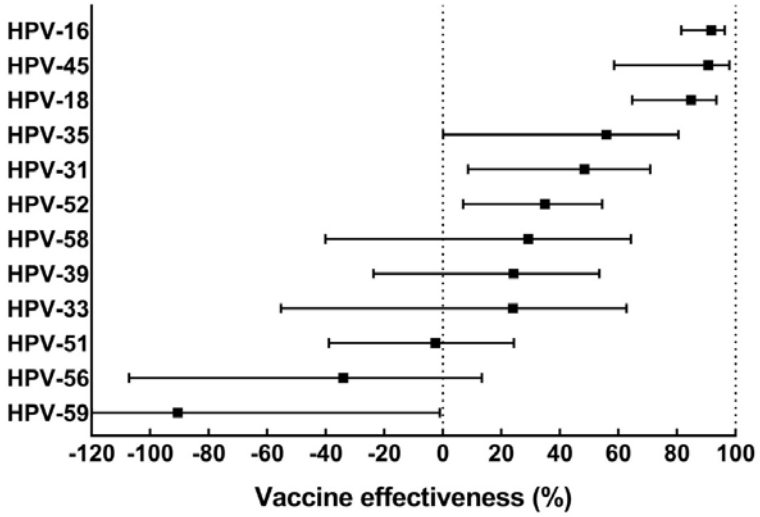

Figure 2.3.6 Vaccine effectiveness against hrHPV types as measured in the PASSYON-study among women eligible for HPV16/18-vaccination

Also, among these vaccine-eligible women in the PASSYON study, the effect of the bivalent HPV-16/18 vaccine on genital HPV-6/11 positivity and AGW was studied, but no impact was found. Relative to unvaccinated women, the adjusted prevalence ratio (PR) for HPV6/11 was 1.02 (95%CI 0.74–1.42) for women vaccinated at least once and 0.90 (95%CI 0.62-1.30) for women vaccinated three times. The crude PR for diagnosis of AGW was 0.67 (95%CI 0.22-2.07) for women vaccinated at least once and 0.64 (95%CI 0.18-2.25) for women vaccinated three times. Adjustment did not change these results. No cross-protective effect of the bivalent vaccine on genital HPV-6/11 positivity was found [193]. The estimate of the effect on AGW is in line with earlier findings [144, 194, 195].

In 2016, a new cohort study (HAVANA2) was initiated among girls born in 2001, who were eligible for vaccination in 2014 at twelve years of age. The primary aim of this study is to monitor the effect on HPV-type distribution amongst girls vaccinated with a two-dose schedule (0, 6 months) and unvaccinated girls. The follow-up for this study is planned for at least five years. Results of the first round of sampling, which was held in September 2016, are expected in 2017.

3 Safety and (adverse) consequences of HPV vaccination

Summary

Local reactions and systemic adverse events are commonly reported after HPV vaccination, but are mostly mild and transient. As of yet, there is no evidence of a statistically significant association with serious adverse events. However, it is important to keep studying new cases to understand the pathogenesis of these events to improve the acceptance of HPV vaccination. So, the ongoing vigilance to ensure the safety of HPV vaccines, in which pre-vaccination morbidity should be taken into account, remains important.
Up to now, no type-replacement has been reported. Furthermore, no evidence has been found for riskier behaviours or higher rates of STIs after HPV vaccination.

3.1 Glossary

Acute
A short-term, intense health effect
Adverse event (AE)
Undesirable experiences occurring after immunization that may or may not be related to the vaccine.
Adverse event following immunization (AEFI)
Any untoward medical occurrence which follows immunization, but which does not necessarily have a causal relationship with the use of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.
Adverse reaction
A classification of AEFI, referring to events caused or precipitated by the vaccine when given correctly, caused by the inherent properties of the vaccine.
Local
Restricted or limited to a specific body part or region.
Mild vaccine reaction
Vaccine reactions that usually occur within a few hours of injection, resolve after a short period of time and pose little medical danger.
Passive surveillance (also referred to/known as spontaneous reporting)
A surveillance system designed to collect adverse events that follow vaccination. This type of surveillance typically relies on health professionals, patients or relatives of patients noticing and reporting adverse events in individuals after vaccination to the NRA or appropriate authority.
Reactogenicity
Being able to produce adverse reactions.
Safety profile
A summary of the evidence on the safety of a medical product, such as a vaccine or drug, under ideal conditions of use, including the incidence of any adverse reactions relative to the number of doses given.

Serious adverse event(SAE)
A regulatory term defined as any untoward medical occurrence following any dose: results in death; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; or is life-threatening.
Solicited data
Data derived from organized collection systems, which include clinical trials, registries, post-approval studies, other patient support and disease management programmes, surveys of patients or health care providers, or information gathering on efficacy or patient compliance.
Systemic
Relating to a system or affecting the entire body or an entire organism (e.g., fever).
Unsolicited data
Data from spontaneous reports, literature reports, other sources, e.g. lay press and those from the Internet or digital media.

3.2 Safety reported in pre-licensure vaccine trials

3.2.1 Safety 2vHPV vaccine

The safety of 2vHPV was evaluated by pooling data from controlled and uncontrolled clinical trials involving 23,952 females that were 9 to 25 years of age in the pre-licensure clinical development programme. In these studies, 13,024 females (9 through 25 years of age) received at least one dose of 2vHPV and 10,928 females received at least one dose of a control (Hepatitis A or Al(OH)3 containing) vaccine [120, 196]. Data on solicited local and general adverse events were collected from subjects or parents using standardized diary cards for seven consecutive days following each vaccine dose (i.e. day of vaccination and the next six days). Unsolicited adverse events were recorded with diary cards for 30 days following each vaccination (day of vaccination and the 29 subsequent days). The reported frequencies of solicited local injection-site reaction (pain, redness and swelling) and general adverse events (fatigue, fever, gastrointestinal symptoms, headache, arthralgia, myalgia and urticaria) within seven days after vaccination in females aged 9 to 25 years are presented in Table 3.2.1.

Table 3.2.1 Rates of solicited local adverse reactions and general adverse events in females 9 to 25 years of age within seven Days of Vaccination (Total Vaccinated Cohorta)[120]

	2vHPV	HAV 360[b] (10-14 years) %	HAV 720[b] (15-25 years) %	Al(OH)3 Control[d] (15-25 years) %
Local adverse reaction	*N=6,669*	*N=1,027*	*N=3,079*	*N=549*
Pain	91.9	64.2	78.0	87.5
Swelling	48.4	25.2	27.6	24.4
Redness	44.3	17.3	19.8	21.3
General adverse events	*N=6,670*	*N=1,027*	*N=3,079*	*N=549*
Fatigue	54.6	42.3	53.7	53.6
Headache	53.4	45.2	51.3	61.4
Gastrointestinal complaints[e]	27.9	24.6	27.3	32.8
Fever	12.9	16.0	10.9	13.5
Rash	9.5	6.7	8.4	10.0
	N=6,119	*N=1,027*	*N=3,079*	-
Myalgia[f]	48.8	33.1	44.9	-
Arthralgia[f]	20.7	19.9	17.9	-
Urticaria[f]	7.2	5.4	7.9	-

[a] Total vaccinated cohort included subjects with at least one documented dose (N).
[b] HAV 360 = Hepatitis A Vaccine control group [360 EL.U. of antigen and 250 mcg of Al(OH)3].
[c] HAV 720 = Hepatitis A Vaccine control group [720 EL.U. of antigen and 500 mcg Al(OH)3].
[d] Al(OH)3 Control = Control containing 500 mcg Al(OH)3.
[e] GI = Gastrointestinal symptoms, including nausea, vomiting, diarrhoea and/or abdominal pain.
[f] Adverse events solicited in a subset of subjects.

Local reactions were reported more frequently with 2vHPV when compared with the control groups; in ≥76% of recipients of 2vHPV, these local reactions were mild to moderate in intensity. Compared with dose 1, pain was reported less frequently after doses 2 and 3 of 2vHPV, in contrast to redness and swelling when there was a small increased incidence. There was no increase in the frequency of general adverse events with successive doses [120].

The frequency of unsolicited adverse events that occurred within 30 days of vaccination (≥1% for 2vHPV and greater than any of the control groups) in females 9 to 25 years of age are presented in Table 3.2.2.

Table 3.2.2 Rates of unsolicited adverse events in females 9 to 25 years of age within 30 days of Vaccination (≥1% For 2vHPV and greater than HAV 720, HAV 360, or 117 Al(OH)3 Control) (Total Vaccinated Cohorta)[120]

	2vHPV (n=6,893)	HAV 360[b] (10-14 years) (n=1,032) %	HAV 720[b] (15-25 years) (n=3,186) %	Al(OH)3 Control[d] (15-25 years) (n=581) %
Headache	5.2	3.3	7.6	9.3
Nasopharyngitis	3.7	5.9	3.4	3.3
Influenza	3.1	1.3	5.6	1.9
Pharyngolaryngeal pain	2.9	2.2	2.7	2.2
Dizziness	2.2	1.5	2.6	3.1
Upper respiratory infection	2.0	6.7	1.3	1.5
Chlamydia infection	1.9	0.0	4.4	0.0
Dysmenorrhea	1.9	1.9	2.3	4.0
Pharyngitis	1.4	2.2	1.8	0.5
Injection site bruising	1.4	0.7	1.8	1.5
Vaginal infection	1.3	0.1	2.2	0.9
Infection site pruritus	1.3	0.6	0.5	0.2
Back pain	1.1	0.7	1.3	3.1
Urinary tract infection	1.0	0.3	1.4	1.2

[a] Total vaccinated cohort included subjects with at least one documented dose (N).
[b] HAV 360 = Hepatitis A Vaccine control group [360 EL.U. of antigen and 250 mcg of Al(OH)3].
[c] HAV 720 = Hepatitis A Vaccine control group [720 EL.U. of antigen and 500 mcg Al(OH)3].
[d] Al(OH)3 Control = Control containing 500 mcg Al(OH)3.

The pooled safety database, which included controlled and uncontrolled trials that enrolled females aged 9 to 25, was searched for new medical conditions indicative of potential, new onset autoimmune diseases (NOADs). Overall, the incidence of NOADs, as well as potential NOADs, in the group receiving 2vHPV was 0.8% (96/12,772) and comparable to the pooled control group (0.8%, 87/10,730) during the 4.3 years of follow-up [120].
The inclusion of the immune-stimulating component MPL in the 2vHPV adjuvant might account for a somewhat higher reactogenicity of the vaccine [197]. No differences were found regarding SAEs. In the Rivera-Medina Phase III – an observer-blind, multi-centre, randomized, parallel group, controlled study – the occurrence of SAEs was similar in both vaccine (1.1%) and control groups (1.3%) [198].

One study evaluated the safety of 2vHPV in boys aged 10-18 years [199]. Healthy males aged 10 to 18 years were randomized (2:1 ratio) to receive HPV-16/18 AS04-adjuvanted vaccine (n = 181) or hepatitis B virus (HBV) control vaccine (n = 89) at 0, 1, and 6 months, and were followed for seven months after the last vaccination. The reactogenicity profiles of the HPV-16/18 AS04 and HBV vaccines were similar, except

that pain and swelling at the injection site were more common in the HPV-16/18 group (see Table 3.2.3).

Table 3.2.3 Incidence of solicited local reactions and solicited general adverse events in healthy males 10 to 18 years reported during the seven-day follow-up period following administration of 2vHPV or HBV vaccines, overall per dose (total vaccinated cohort)

	2vHPV (n=523)		HBV Control (n=259)	
	%	95% CI	%	95% CI
Local adverse reactions				
Pain	72.3	68.2-76.1	22.0	17.1-27.6
Redness	16.6	12.5-20.1	11.2	7.6-15.7
Swelling	10.7	8.2-13.7	3.1	1.3-6.0
General adverse events				
Myalgia	27.0	23.2-31.0	12.4	8.6-17.0
Fatigue	24.9	21.2-28.8	23.6	18.5-29.2
Headache	21.2	17.8-25.0	17.4	13.0-22.5
Gastrointestinal	11.7	9.0-14.7	7.3	4.5-11.2
Fever	9.9	7.5-12.8	8.1	5.1-12.1
Arthralgia	6.7	4.7-9.2	5.0	2.7-8.4
Rash	3.6	2.5-5.6	1.9	0.6-4.4
Urticaria	0.8	0.2-1.9	0.8	0.1-2.8

CI = confidence interval; HBV = hepatitis B vaccine.

The frequency of unsolicited symptoms reported during the 30-day post-vaccination period following each dose was similar between groups: 15.7% and 15.6% in the 2vHPV and control HBV vaccine groups, respectively [199]. Two SAEs occurred in two participants that received 2vHPV (Crohn's disease and epilepsy). A boy diagnosed with Crohn's disease had symptoms that may have been related to the disease prior to the first dose of the vaccine and a boy diagnosed with epilepsy had a family history of this condition. Both events were considered by the investigator to be unrelated to the study vaccination.

In general, local reactions and general adverse events after 2vHPV vaccination were reported more by females than by males.

3.2.2 *Safety 4vHPV vaccine*

A study of Reisinger et al [200] showed that headache, fever and pharyngeal pain were reported as the most common systemic AEs following 4vHPV vaccination; however, there was no significant difference between vaccination groups and control groups. There were very few serious vaccine-related AEs (<0.1%) and they were no more frequent than they were in those receiving a saline placebo.
Another review with meta-analysis [201], including six clinical trials, described similar results, demonstrating that, overall, the incidence of SAEs and deaths was balanced between the vaccine and control groups (odds ratio for SAEs 0.998, 95% CI 0.87 – 1.14; for death 0.91, 95% CI 0.39 – 2.14). SAEs considered to be related to the vaccine included bronchospasm, gastroenteritis, headache, hypertension and pain at the injection site or impaired joint movement in the injected limb. Most

deaths were reported as accidental and none of the deaths was considered attributable to the vaccine.

Prior to approval of the 4vHPV vaccine, the FDA evaluated the safety of the vaccine in females by pooling data from controlled and uncontrolled clinical trials [122]. The most reported local reactions and general adverse events are shown in Table 3.2.4.

Table 3.2.4 Rates of solicited local adverse reactions and general adverse events in females aged 9 to 26 [122]a

	4vHPV %	AAHS Control[b] %	Saline placebo %	AAHS Control or Saline Placebo %
Local adverse reaction *(1-5 days post-vaccination)*	*N=5,088*	*N=3,470*	*N=320*	
Pain	83.9	75.4	48.6	
Swelling	25.4	15.8	7.3	
Redness	24.7	18.4	12.1	
Pruritus	3.2	2.8	0.6	
Bruising	2.8	3.2	1.6	
General adverse events *(1-15 days post-vaccination)*	*N=5,088*			*N=3,790*
Headache	28.2			28.4
Pyrexia	13.0			11.2
Nausea	6.7			6.5
Dizziness	4.0			3.7
Diarrhea	3.6			3.5
Vomiting	2.4			1.9
Cough	2.0			1.5
Toothache	1.5			1.4
Upper respiratory tract infection	1.5			1.5
Malaise	1.4			1.2
Arthralgia	1.2			0.9
Insomnia	1.2			0.9
Nasal congestion	1.1			0.9

[a] The local adverse reactions that were observed among recipients of 4vHPV were at a frequency of at least 1.0%.
[b] AAHS control = Amorphous Aluminum Hydroxyphosphate Sulphate

Safety data on 4vHPV in males taken from seven clinical trials included 5,396 men aged 9-26 years that received 4vHPV, aluminum-containing control (AAHS) or a saline placebo [122]. Table 3.2.5 shows the rates of the most commonly reported local reactions and systemic events in males aged 9 to 26.

Table 3.2.5 Rates of solicited local adverse reactions and general adverse events in males aged 9 to 26 [122]a

	4vHPV %	AAHS Control[b] %	Saline placebo %	AAHS Control or Saline Placebo %
Local adverse reaction *(1-5 days post-vaccination)*	*N=3,093*	*N=2,029*	*N=274*	
Pain	61.4	50.8	41.6	
Swelling	13.9	9.6	8.2	
Redness	16.7	14.1	14.5	
Hematoma	1.0	0.3	3.3	
General adverse events *(1-15 days post-vaccination)*	*N=3,093*			*N=2,303*
Headache	12.3			11.2
Pyrexia	8.3			6.5
Oropharyngeal pain	2.8			2.1
Diarrhoea	2.7			2.2
Nasopharyngitis	2.6			2.6
Nausea	2.0			1.0
Upper respiratory tract infection	1.5			1.0
Abdominal pain upper	1.4			1.4
Myalgia	1.3			0.7
Dizziness	1.2			0.9
Vomiting	1.0			0.8

[a] The local adverse reactions that were observed among recipients of 4vHPV were at a frequency of at least 1.0%.
[b] AAHS control = Amorphous Aluminum Hydroxyphosphate Sulphate

In both female and male study populations (n=29,323), 0.04% of the reported serious systemic adverse reactions were judged to be vaccine-related by the study investigator. The proportions of persons reporting a serious adverse event were similar in the vaccine and placebo groups, as were the types of serious adverse events reported. SAEs after 4vHPV vaccination, regardless of causality, concerned headache (n=3), gastroenteritis (n=3), appendicitis (n=5), pelvic inflammatory disease (n=3), urinary tract infection (n=2), pneumonia (n=2), pyelonephritis (n=2), pulmonary embolism (n=2), bronchospasm (n=1) and asthma (n=2) [122, 202].
During the course of the trials, 21 deaths (0.1%) occurred among persons in the 4vHPV groups and 19 (0.1%) among persons in the control or placebo groups. None of the deaths was considered to be vaccine-related [122]. Furthermore, information was collected on new medical conditions that occurred during follow-up period of up to 3 years. No statistically significant differences were found between vaccine and control/placebo recipients for the incidence of conditions potentially indicative of autoimmune disorders (i.e. 2.3% for both groups in women and 1.5% for both groups in men) [122].

In general, local reactions and general adverse events after 4vHPV vaccination were reported more by females than by males.

3.2.3 Safety 9vHPV vaccine

The safety of 9vHPV was evaluated in approximately 16,000 males and females. The most commonly reported adverse reactions in girls and women were injection site pain (about 90%), swelling (40%), redness (34%) and headaches (15%) [124]. In boys and men, 63-72% reported injection site pain, 20-27% swelling and 21-25% redness. Several trials showed that administration of a three-dose regimen of 9vHPV vaccine was generally well-tolerated in males and females aged 9-26 [153, 154, 173, 174], although the incidence of injection-site swelling in girls was higher in the 9vHPV group compared with a 4vHPV group (47.8% vs. 36.0%) [153]. In another trial in men aged 16-26, more participants reported injection-site pain (77.8% vs. 70.2%) and swelling (14.5% vs. 9.3%) after receiving 9vHPV compared with 4vHPV, although these differences did not reach statistical significance [203]. Concomitant administration of 9vHPV and other childhood vaccines, (i.e. diphtheria, tetanus, pertussis and poliomyelitis vaccines, meningococcal vaccines and Tdap vaccines) also demonstrated a good safety profile [204, 205]. Serious adverse events were collected in several clinical studies. Out of the 15,705 individuals who were administered 9vHPV, 2.3% of the population reported a SAE. As a comparison, of the 7,378 individuals who were administered 4vHPV, 2.5% of the population reported a SAE [124]. Four 9vHPV recipients each reported at least one SAE that was determined to be vaccine-related. The vaccine-related serious adverse reactions were pyrexia, allergy to vaccine, asthmatic crisis and headache. Furthermore, in these clinical trials subjects receiving 9vHPV were also evaluated for new medical conditions that are potentially indicative of a systemic autoimmune disorder. In total, 2.2% (351/15,703) of 9vHPV recipients and 3.3% (240/7,378) of 4vHPV recipients reported new medical conditions that are potentially indicative of systemic autoimmune disorders, which were similar to rates reported following AAHS control or saline placebo in historical clinical trials. Across the studies, five deaths occurred in the 9vHPV group; none were assessed as vaccine-related [124].

3.3 Monitoring of adverse events in the post-vaccination era

Adverse events were extensively monitored during the catch-up campaign for 13 to 16-year-old girls and the introduction of HPV vaccination into the NIP for 12-year-old girls in the Netherlands in 2009 and 2010, respectively. All immediately occurring adverse events at locations during mass vaccination were registered and a questionnaire study was performed into the tolerability of the vaccine [206-208]. Furthermore, continuous monitoring of adverse events has been put in place by means of an enhanced passive surveillance system. From 2011 onwards, this passive surveillance system has been managed by the National Centre for Pharmacovigillance Lareb [209, 210]. Before 2011, this passive monitoring system was maintained by the RIVM [211]. Moreover, following the change in schedule in 2014, from a three-dose schedule to a two-dose schedule for girls up to 14 years of age, a questionnaire study was conducted into the tolerability of the vaccinations [191]. In the following sections, the results of adverse events monitoring are presented.

3.3.1 *Passive reports on adverse events in the Netherlands*

Most reports of adverse events following HPV immunization (AEFIs) to the Netherlands Pharmocovigilance Centre Lareb concern short-term AEFIs, and these are mostly stable over the years (see Table 3.3.1) [212-216].

Table 3.3.1 Reported adverse events after HPV vaccination per year

Vaccines	Total	2010	2011	2012	2013	2014	2015
Death	**0**	0	0	0	0	0	0
Injection site reactions	**119**	19	16	10	22	15	37
Abnormal body temperature	**127**	34	9	21	27	15	21
Infections[a]	**33**	2	2	10	4	1	14
Malaise and fatigue	**317**	4	10	43	24	18	218
Allergic reaction	**12**	0	2	3	1	1	5
Disorders or the immune system[b]	**6**	0	1	0	0	0	5
Crying[c]	**5**	0	0	0	0	2	3
Haematological disorders	**1**	0	0	0	0	0	1
Gastrointestinal complaints	**156**	10	3	29	26	25	63
Respiratory symptoms	**23**	4	1	0	2	2	14
Cardiovascular diseases	**33**	0	0	0	3	0	30
Muscle and joint disorders	**122**	0	4	8	22	17	71
Skin symptoms	**65**	7	11	9	14	8	16
Discoloured arms	**5**	3	0	2	0	0	0
Headache/dizziness	**355**	7	7	39	43	43	216
Complaints of reproductive organs	**20**	4	0	0	0	0	16
Faints	**114**	18	7	17	9	8	55
Fits	**7**	2	1	1	1	0	2
Other disorders of the nervous system	**51**	2	3	8	5	8	25
Other disorders	**65**	14	5	6	12	3	25

[a] All reports about infections which are probably, possibly or certainly related to the vaccination.
[b] rheumatoid gastritis (n=1), immune thrombocytopenic purpura (n=1), autoimmune thyroiditis (n=1), Type I diabetes mellitus (n=1), Basedow's disease (n=1), Thrombocytosis (n=1).
[c] (sudden) screaming, non-consolable and lasting for three hours or more.

However, the increase in reported AEFIs in 2012 and especially in 2015 compared with the other years is remarkable. The majority of these reports concerns long-lasting AEFIs that were received after media attention in these years focused on the HPV vaccine [217]. In the same period, there was media attention in Denmark concerning conditions assumed to be related to HPV vaccination: complex regional pain syndrome (CRPS) and postal orthostatic tachycardia syndrome (POTS). At the end of July 2015, Lareb published an update of the previous overview of all AEFIs reported in relation to 2vHPC. Following this release, concerns about the safety of 2vHPV were picked up by national media. In the month following this media attention, Lareb received more than one-hundred reports on 2vHPV. Lareb enhanced the clinical documentation level of both the newly received and the older reports concerning long-lasting (duration of 2 months or more) AEFIs by obtaining additional information through intensive follow-up.

The reports concerned vaccinations given over the whole period since the start of the programme. Since Lareb depends on spontaneous reports, it is not possible to estimate the actual prevalence of long-lasting AEFIs after vaccination with 2vHPV.

Since the introduction of the HPV vaccine in the NIP in 2009, Lareb has received 1,436 reports of possible AEFIs following 2vHPV, including 346 reports of long-lasting AEFIs with a duration of 2 months or more. The reported rate of long-lasting AEFIs per birth cohort is constant, about 5 per 10,000 vaccinated girls. Fatigue was the most frequently reported long-lasting AEFI (see Table 3.3.2). Several combinations of frequently reported AEFIs were found, but there was no consistent combination pattern in all the reports of long-lasting AEFIs [217]. One of the most reported combinations of long-lasting AEFIs concerns fatigue combined with headache and musculoskeletal discomfort. This combination of complaints, including the fact that no known medical explanation was found, are partially compatible with the criteria for chronic fatigue syndrome used by the Dutch Institute for Healthcare Improvement (CBO) concerning the diagnosis, treatment, support and assessment of patients with chronic fatigue syndrome (CFS) [218]. Although some reports concern symptoms that could be indicative of POTS or CRPS, in none of them were there any indications for these diagnoses.

Table 3.3.2 Top 10 reported long-lasting AEFIs associated with 2vHPV. Date received: 01-01-2009 to 31-10-2016.

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

AEFI = adverse event following immunisation.

It is difficult to estimate the latency accurately, since most reports of long-lasting AEFIs have a reporting delay of three to six years and symptoms often gradually develop. There appeared to be no typical interval: onset varied from days to months and even a few years after vaccination.
Lareb also investigated whether there could be a batch-related problem. Based on information gathered on the size of the batches, the geographical distribution of the batches and the years in which the batches were used, a batch-related problem did not seem likely.
Overall, Lareb concluded that a causal relation between 2vHPV vaccination and long-lasting symptoms could not be confirmed nor

excluded based on the analysis of these reports. In order to study whether long-lasting fatigue occurs more often in vaccinated girls than in unvaccinated girls and in order to determine the presence and strength of a causal relationship, Lareb recommended epidemiological research.

3.3.2 Acute events in the Netherlands

During the vaccination sessions in 2009 (catch-up campaign for 13 to 16-year-old girls) and in 2010 (12-year-old girls), report forms were distributed at all vaccination locations for the recording of immediate adverse events. Two separate forms were distributed: one form was designed for the registration of each immediate AE individually; the other form collected aggregated information on the total number of adverse events at the vaccination site, together with the total number of administered vaccines during the vaccination session.

In 2009, a total of 1,107 reports of immediately occurring adverse events at locations of mass vaccination from 408,662 administered doses were received. This resulted in a reporting rate of 27.1/10,000 administered doses [208].
The most reported immediately occurring event was presyncope and syncope with a reporting rate of 16.8 per 10,000 administered doses (n=688). Jerking and vomiting coincided with presyncope and syncope in 81% and 71%, respectively. The reporting rate of other vasovagal symptoms was 7.9 per 10,000 administered doses (n=322). Rash and dyspnea were reported in 0.3 and 1.3 per 10,000 administered doses. No anaphylactic shock was reported.
An injury was reported 28 times, in all but one case related to presyncope and syncope. Twelve girls received assistance from ambulance staff because of syncope and/or dizziness, three times because of injury. An ambulance was routinely present at the locations of mass vaccination.

In 2010, information was available on 168,134 administered doses. In total, 130 reports of immediate events were received, resulting in a reporting rate of 7.7 per 10,000 administered doses [207].
As in 2009, presyncope or syncope was the most reported event, with a reporting rate of 5.8 per 10,000 administered doses (n=97). Jerking (n=5) and vomiting (n=2) only occurred in relation to presyncope or syncope. Other vasomotor symptoms were reported with a frequency of 2.0 per 10,000 administered doses (n=33). Only one girl reported skin symptoms and dyspnea was reported three times. No anaphylactic shock was reported.
Injury was reported 10 times, all related to syncope. The ambulance staff assisted two girls, one of which had an injury.

3.3.3 Tolerability in the Netherlands

The tolerability of the vaccine was measured using online questionnaires with questions concerning the occurrence of local reactions and systemic adverse events in the seven days following vaccination. Also, information was recorded on the severity and duration of the adverse events. In addition, the occurrence of symptoms in the week before vaccination was confirmed.

Three questionnaire studies were performed; the first during the catch-up campaign for 13 to 16-year-old girls in 2009, the second during the first year of introduction of the HPV vaccine into the NIP in 2010 and the third during the first year of the change from a three-dose schedule to a two-dose schedule in 2014. The occurrence of local reactions and systemic adverse events is presented in Figure 3.3.1 [191, 207, 208, 219]

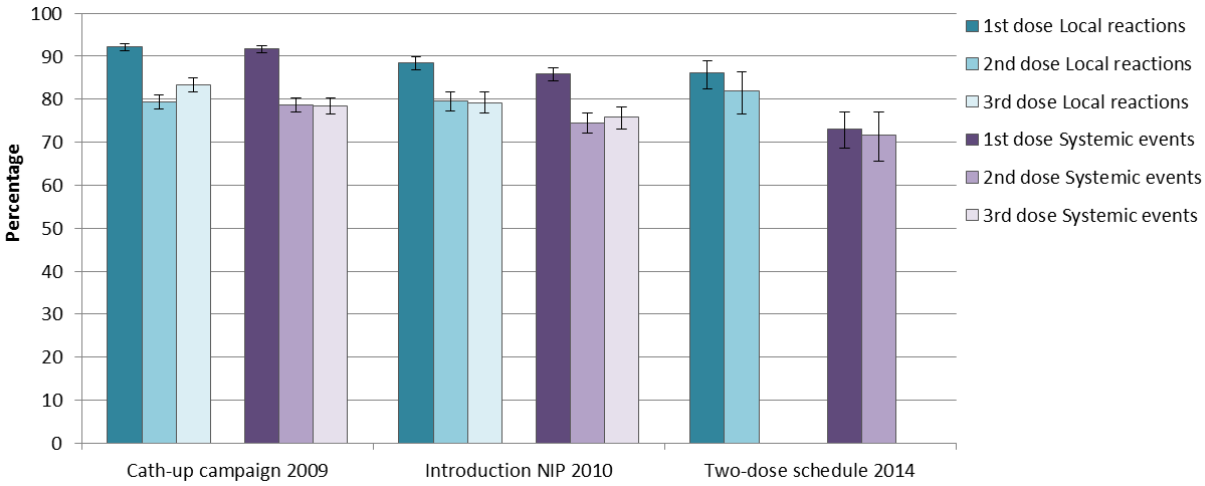

Figure 3.3.1 Occurrence of local reactions and systemic adverse events following the catch-up campaign for 13 to 16-year old girls (2009), the introduction of HPV vaccination in the NIP for 12-year-old girls (2010) and the change to a two-dose schedule (2014)

NIP = National Immunisation Programme.

Overall, between 12% and 22% of the girls reported pronounced local reactions. The most reported local reactions were pain (70-86%) and reduced use of the arm (49-66%). Myalgia was the systemic event most reported (56-73%) after vaccination. Fatigue and headache were also frequently reported systemic events after vaccination, as well as in the week before vaccination (Figure 3.3.2). During the catch-up campaign, older girls reported a higher proportion of adverse events compared with the younger girls (OR 1.05, 95% CI 0.68-1.63 for cohort 1996 up to OR 4.95, 95% CI 1.52-16.12 for cohort 1993 compared to cohort 1997). Furthermore, girls with local reactions reported the occurrence of systemic symptoms more often than girls without local reactions (83-92% versus 58-64%).

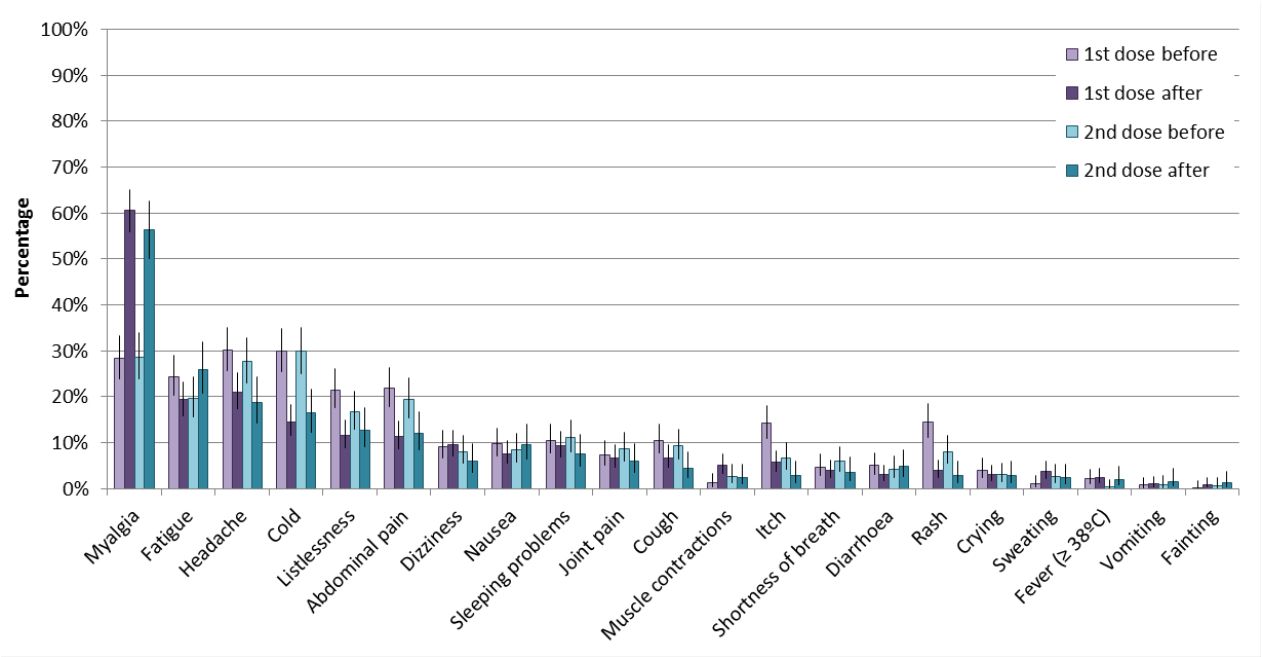

Figure 3.3.2 Occurrence of systemic events before and after the two-dose schedule (2014)

In addition, the tolerability of the two-dose schedule (0, 6 months) was compared with that of the three-dose schedule (0, 1, 6 months) for 12-year-old girls. For the dose at six months, the tolerability was comparable for both schedules, except for mild pain, which was reported more frequently after the last dose of the two-dose schedule. In total, the change from a three-dose schedule to a two-dose schedule, i.e. the administration of one dose less and more time between doses, resulted in 32% fewer local reactions and 39% fewer systemic events, with a comparable number of reactions for the doses at six months.

3.3.4 *Additional research on adverse events in the Netherlands following early warning alerts*

In 2014, additional research was conducted on the possible association between HPV vaccination and migraine, because migraine had been reported as a relevant event in the passive surveillance system [220]. Post-vaccination incidences were found to be slightly higher than pre-vaccination incidences, but not statistically significant (IRR 1.14, 95% CI 0.82-1.62). Yet an increase in incidence in the same period was also found in boys, even though they were not vaccinated (IRR 1.21, 95% CI 0.77-1.97). No significantly higher risk of migraine was found in the months following vaccination compared with the risk in unvaccinated girls. Furthermore, using self-controlled case series analysis, no statistically significant elevated risk of migraine in four defined high-risk periods versus non-high-risk periods was found (risk estimates ranged between 2.1 (95% CI 0.26-16.7) and 6.3 (95% CI 0.80-49.1). The number of cases in this study, however, was very low (n=11).

As a result of the increased reporting of long-lasting fatigue in the passive surveillance system, a study is currently being conducted into the possible relationship between HPV vaccination and long-lasting fatigue (≥ 6 months). Girls with complaints of fatigue were selected from

a GP registration database and validated manually. Cases were asked for informed consent to link their medical data with HPV vaccination data. In this research, age-specific incidences of long-lasting fatigue in the period following introduction of vaccination will be compared with incidences before introduction of vaccination. Furthermore, a self-controlled case series analysis will be done for vaccinated cases, in which incidence in the high-risk period (1 year after vaccination) will be compared with incidence in the non-risk periods. A total of 49 girls have given consent to link the GP data with their vaccination status. Results are expected in the first quarter of 2017.

3.3.5 International monitoring of adverse events and emerging issues

3.3.5.1 Adverse Events (AEs)

Vaccines continue to be monitored for safety after they are licensed. Local symptoms, which include pain, redness and swelling at the injection site, are the most frequent AEs reported for both 2vHPV and 4vHPV in the post-licensure phase [221]. Pain was usually the most frequently reported local symptom after each dose – reported more frequently in people who were vaccinated with 2vHPV than in those vaccinated with 4vHPV – followed by redness and swelling. Generally, the incidence of AEs per dose did not increase with increased number of doses [222, 223]. Headache and fatigue were the most common vaccine-related systemic AEs [224, 225]. Other general symptoms included vasovagal syncope, gastrointestinal symptoms, arthralgia, myalgia, rash, fever and urticarial (which are generally monitored by different types of surveillance systems after vaccination), irrespective of the type of vaccine [219, 226-228].
The rates of local reactions and systemic events reported for males are comparable to or somewhat lower than those reported for females [120, 124, 170, 202, 229].

Pregnancy outcomes have received special attention, given the target ages of catch-up vaccination programmes. Although, specific studies of the vaccines in pregnant women have not been conducted. Postmarketing pregnancy registries have been established to evaluate pregnancy outcomes following immunization occurring within 1 month before the last menstrual period or at any time during pregnancy. For 2vHPV, during the clinical development programme, a total of 10,476 pregnancies were reported that included 5,387 women who had received 2vHPV. Overall, the proportions of pregnant subjects that experienced specific outcomes (e.g. normal infants, abnormal infants, including congenital anomalies, premature birth and spontaneous abortion) were similar between the treatment groups [138]. For 4vHPV, during the clinical development programme, 3,819 women (vaccine = 1,894 vs. placebo = 1,925) reported at least one pregnancy. There were no significant differences in types of anomalies or the proportion of pregnancies with an adverse outcome in 4vHPV and placebo-treated individuals. These data from pregnant women (more than 1,000 exposed outcomes) indicated no malformations nor any foeto/neonatal toxicity [116]. Also for 9vHPV, a large amount of data on pregnant women (more than 1,000 pregnancy outcomes) indicated no malformations nor any foeto/neonatal toxicity. The data on 4vHPV administered during pregnancy did not indicate any safety signal [117]. Nevertheless, as a precautionary measure, it is preferable to avoid the

use of HPV vaccination during pregnancy [116, 117, 138]. A pooled analysis of the PATRICIA and Costa Rica Vaccine Trials found no significant increase in miscarriages in the 2vHPV group (11.5%) compared with the control group (10.2%) [230]. However, it is necessary to follow up a currently nonsignificant signal of an increased rate of miscarriage in pregnancies conceived within three months of 2vHPV vaccination.
In a combined analysis of phase III trials involving 4vHPV, the proportions of women with live births, spontaneous abortions and congenital abnormalities were similar in the vaccine and control groups [123, 231]. For example, the rate of spontaneous abortion was 21.9% and 23.3% in the 4vHPV and control groups, respectively. The congenital abnormalities observed were diverse and consistent with those generally seen in young women. Several post-licensure safety studies have been conducted or are ongoing [227, 232, 233]. To date, the findings are consistent with those of the clinical trials, showing no increased risk for adverse events.

3.3.5.2 Serious Adverse Events (SAEs)

SAEs are generally defined as any medical occurrence that is life-threatening, that requires or prolongs hospital admission or that results in disability, incapacity or death. Studies that evaluated the incidence of SAEs concluded that none of the reported SAEs were considered as related to any HPV vaccination [226, 234]. In the following sections, we discuss specific events that have been reported in the literature as potentially related to or triggered by HPV vaccination.

3.3.5.2.1 POTS/CRPS

From 2013 and onwards, the Danish Health and Medicines Authority has received a number of reports regarding suspected serious adverse reactions after vaccination with 4vHPV. Some of the first cases reported had been diagnosed with POTS. A number of additional serious cases were without diagnoses, but included symptoms that resembled cases of POTS, such as long-lasting dizziness, headache, syncope and fatigue. Denmark raised the signal, informing the EMA Pharmacovigilance Risk Assessment Committee (PRAC) in September 2013. Based on the data and number of cases at that point in time, the PRAC concluded that the issue should be evaluated in the yearly periodic safety update reports (PSURs) for 4vHPV.
During the same period, a signal was raised with respect to CRPS. With CRPS, the most common symptoms are severe pain, swelling and changes in the skin temperature and the colour of the arms or legs, but it may also include amongst other symptoms, such as headache, general fatigue, coldness of the legs, limb pain and weakness. The cases of CRPS were mostly reported for 2vHPV and most case reports originated from Japan. Following a review of all available data on CRPS, PRAC concluded in 2014 that the available evidence did not support a causal association and that the issue should be reviewed through the PSURs. In the PSUR assessment from December 2014, it was concluded that, with respect to both POTS and CRPS, a causal relationship could not be ruled out.

Various publications in recent years have raised potential signals of concern regarding adverse reactions after HPV vaccination [235-238].

Based on the signals raise with respect to POTS and CRPS, as well as the description of case reports of other syndromes, it was found that very similar patterns of symptoms appearing after HPV vaccination were described, despite the differences in diagnoses. It is plausible that similar types of cases would receive different diagnoses, depending on the national clinical setting, and that a safety signal might be present to be observed, but would potentially be diluted due to different diagnoses in different countries.
The design of studies such as theoretical reviews or case series without non-vaccinated control groups only enables hypotheses of possible mechanisms to be generated, but provides no firm knowledge of the causal association existing between vaccination and reported reactions. Since many of the symptoms are seen in the background target population, it is a significant challenge to distinguish causal from temporal association.

Studies designed to elucidate whether excess risk of various diseases is present in the vaccinated population have been published [239-243]. The risk of chronic fatigue syndromes in relation to the 2vHPV vaccine was investigated using database records and reported adverse events in the UK. This self-controlled case series, which involved 187 girls, showed no evidence of an increased risk of fatigue syndromes in the year following the first vaccination (IRR 1.07; 95%CL 0.57-2.00) [241]. As mentioned, studies using registers to identify outcome measures are limited because the outcome is highly dependent on diagnoses. The syndromes suspected as reactions to HPV vaccination are often difficult to diagnose and there is an overlap in symptoms between diagnoses. Therefore, the UK study initially used a broad definition with subsequent sensitivity analyses, restricting the codes used to identify cases. Still, neither of these analyses found an association between the vaccine and fatigue syndromes.

Taking into account the totality of the available information, the PRAC concluded in November 2015 that the evidence did not support the theory that HPV vaccines cause CRPS or POTS [244]. The Nordic Cochrane Center criticized the way in which this safety review was conducted [245]. In a point-to-point response, the EMA refuted a number of these allegations [246]. However, according to the Nordic Cochrane Center, its complaints to the EMA were met with replies that did not fully address their concerns and therefore they complained to the EU ombudsman over maladministration at the EMA in relation to the safety of the HPV vaccines [247]. The ombudsman has not yet ruled. In the meantime, Denmark has launched several studies to evaluate any causal relationship between these symptoms and HPV vaccination [248]. In a recent study, Mølbak et al showed that 316 cases with reports of suspected severe adverse reactions following HPV vaccination had increased care-seeking in the two years before receiving the first HPV vaccine, compared with 163,910 controls [249]. According the investigators, the observed pre-vaccination excess morbidity and excess care-seeking does not rule out the possibility that, in certain situations, the vaccine may have triggered a course that resulted in deterioration of symptoms in some individuals in a potentially vulnerable subpopulation. They emphasize that any conclusion as regards the safety of the vaccine should be taken based on an understanding of the characteristics of the

group from which adverse events were reported. Therefore, pre-vaccination morbidity should be taken into account in the evaluation of safety signals.

3.3.5.2.2 Venous Thromboembolism

In 2011, a prospective cohort study showed an increased risk for venous thromboembolism (VTE) among girls receiving at least one dose of 4vHPV [250]. However, the study was unable to determine whether the VTE observed was attributable to known risk factors, or whether these were effect modifiers of the association between 4vHPV and VTE. Females may have other risk factors for VTE (contraceptive use, family risk, etc.). The population of young women that frequently use hormonal contraceptives overlaps with those that receive HPV vaccines and, as such, coincidental occurrence of VTE among HPV recipients may be anticipated [227]. In addition, several post-licensure studies did not identify safety signals with respect to venous thromboembolism events after 4vHPV had been administered [239, 251-253].

3.3.5.2.3 Other auto-immune diseases

Since the introduction of HPV vaccination in national immunization programmes, concerns have been raised about autoimmune and neurological conditions being triggered by HPV vaccination.
In 2011, Chao and colleagues at the Kaiser Permanente Vaccine Study Center in Oakland, California evaluated 189,629 women of all ages who had received at least one dose of 4vHPV between 2006 and 2008 and compared the incidence of autoimmune diseases in these women vs the incidence in women who hadn't received the vaccine [240].
Investigators found no statistically significant differences between the vaccinated and unvaccinated groups with respect to the incidence of immune thrombocytopenia, autoimmune hemolytic anemia, SLE, rheumatoid arthritis, juvenile rheumatoid arthritis, type 1 diabetes, Hashimoto disease, Graves disease, multiple sclerosis, acute disseminated encephalomyelitis, Guillain-Barré Syndrome, neuromyelitis optica, optic neuritis or uveitis.
Among 997,585 girls aged 10-17 years in Denmark and Sweden, Arnheim-Dahlstrom observed a significantly increased finding of three outcomes (Behcet's syndrome, Raynaud's disease, and type 1 diabetes), but further assessment showed no consistent evidence for a plausible causal association; firstly, because these risk signals were relatively weak and, secondly, no temporal relationship between vaccine exposure and outcome was evident [239]. Furthermore, no differences were found between the vaccinated and unvaccinated groups in the incidence of thyroid, gastrointestinal, musculoskeletal, systemic, hematologic, dermatologic or neurologic autoimmune events. Within the same study setting, no causal relationships were found between 4vHPV and demyelinating diseases [243].
In 2014, Grimaldi-Bensouda et al, in collaboration with investigators from 113 medical centres throughout Europe, performed a case-control study matching 211 cases of autoimmune diseases among females aged 14-26 years to 875 controls [242]. Investigators found no evidence for an increased risk of idiopathic thrombocytopenic purpura, multiple sclerosis, Guillain-Barré syndrome, connective tissue disorders (SLE, rheumatoid arthritis or juvenile arthritis), type 1 diabetes or autoimmune thyroiditis following vaccination with 4vHPV.

Vichnin et al published a summary of published, post-licensure 4vHPV safety data from active and passive surveillance [254]. No increase in the incidence of SAEs such as autoimmune diseases, anaphylaxis and stroke was found compared with background rates. Also, in a nationwide study conducted in Sweden, 4vHPV vaccination was not associated with an increased incidence of new-onset autoimmune disease in girls and women with pre-existing autoimmune disease [255]. On the other hand, Pellegrino et al comprehensively analysed all case reports and studies dealing with either the onset of an autoimmune disease in vaccinated subjects or the safety of vaccination in patients with autoimmune diseases in order to define the role of the HPV vaccines in these diseases and hence their safety [256]. They concluded that solid evidence of a causal relationship was provided in a few cases in the examined studies. In conclusion, several studies found no evidence of a statistically significant association with many post-vaccination events, while some point to an incidental relationship between vaccination and symptoms, possibly in individuals already at risk. Nevertheless, findings of increased autoimmune and neurological risks need to be investigated further in studies with a longer follow-up time, a validation of outcomes and data regarding the time of onset and the individuals at risk. As a result, on-going vigilance with respect to the safety of HPV vaccines remains important. In addition, pre-vaccination morbidity should be taken into account in the evaluation of vaccine safety signals.

3.4 Type replacement and unmasking

When measuring vaccine effectiveness and impact, it is important to discriminate between events known as type replacement and unmasking. By type replacement we mean that when vaccination protects against specific pathogen types, different types of the same species emerge and fill the vacant niche, leading to an increased prevalence of non-vaccine types that may also cause disease. Unmasking on the other hand, means that the new type was already present but remained undetected in diagnostics, e.g. due to low-density presence or due to competition with the high prevalent vaccine type. When a high prevalent type is diminished or eradicated by the vaccine, low prevalent types now become apparent, as has been shown for pneumococcal vaccines [257, 258]. This could be reported as type replacement erroneously, as the less prevalent type was already present in the first place, albeit at relatively non-detectable levels. Unmasking is highly dependent on the test used, as different tests have different detection properties for specific types of a pathogen.
For HPV genotyping, many of the assays that are available are broad-spectrum assays. These are generally based on an initial consensus PCR amplifying a small DNA fragment of a broad range of HPV types. Each of these consensus PCRs has a different clinical and analytical relevance [259]. Furthermore, each assay has different specific sensitivities for individual HPV types. As HPV vaccination will lead to a decrease in multiple HPV infections due to the reduction of at least HPV16 and -18, an apparent artificial increase in prevalence of certain non-vaccine types could be observed in the post-vaccination era. This could be explained by unmasking events.
Recently, the unmasking of HPV52 has been shown following testing with a specific HPV test [260]. Also in a recent population-based HPV

prevalence study conducted in the UK, an increase of certain non-vaccine types in a vaccinated population was attributed to unmasking and not to true type replacement [185, 261].
For HPV, no type replacement has been described to date, although mathematical and epidemiological modelling has shown that it could theoretically be possible [262, 263].

In summary, both type-replacement and unmasking are (at least theoretically) possible consequences of HPV vaccination. Close monitoring of cohorts containing both vaccinated and non-vaccinated participants could enable the detection of such events at an early stage.

3.5 Sexual behaviour

During HPV vaccine introduction, concerns were raised that implementation of HPV vaccination could lead to higher sexual risk behaviour. A systematic review found no evidence for riskier behaviours or higher rates of STIs after HPV vaccination [264]. This was also shown in a Dutch cohort study that asked both vaccinated and unvaccinated girls about their knowledge of HPV and their sexual behaviour. No difference in condom use with either a casual partner (aOR 0.85, 95% CI 0.51-1.44) or a steady partner (aOR 0.94, 95% CI 0.57-1.56) was reported by vaccinated participants in comparison with unvaccinated participants [191, 265].

4 Acceptance of vaccination

Summary

Vaccination coverage in the Netherlands for 12-year-old girls increased from 56% (birth cohort 1997) to 61% (birth cohort 2001/2002), while in the catch-up programme performed in 2009 (birth cohort 1993-1996) the uptake was 52%. Uptake among Dutch girls was associated with both demographic characteristics (religion, ethnicity, SES) and with psychosocial characteristics (such as attitude, beliefs about safety, effectiveness, trust, habits, anticipated regret).
In countries where HPV vaccination for boys has been introduced, the HPV vaccination coverage for boys has been somewhat lower than for girls. An explanation for this might be that the HPV vaccination of males is thought to be less necessary by both parents and vaccination healthcare providers and that there are differences in knowledge and attitudes with regard to vaccinating girls versus boys. The highest HPV vaccination coverage was observed in countries in which the vaccine is given for free and is administered at school. Factors associated with vaccine acceptability are more or less similar for boys and girls and their parents. Important factors associated with a high intention to vaccinate are a positive attitude, positive beliefs that the HPV vaccination is safe and effective and high perceived influence of important others on HPV vaccination intention (i.e. high social norms).

4.1 Vaccine uptake among girls in the Netherlands

In January 2010, 2vHPV vaccination (Cervarix, GSK) was introduced for girls aged 12 (born on or after 1 January 1997). In addition, prior to the start of these annual vaccination campaigns, there was a catch-up campaign for birth cohorts born between 1 January 1993 and 31 December 1996 (13 to 16-year-olds). Girls were offered three doses of 2vHPV vaccine at 0, 1 and 6 months. In 2014, the number of doses of 2vHPV vaccine offered was reduced from three to two doses at 0 and 6 months for girls born on or after 1 January 2001.
Participation of the first birth cohort 1997, measured in 2012, was 56.0%, which increased to 61.0% in 2015. In 2016 (birth cohort 2001), the participation for the 2vHPV vaccination against cervical cancer remained unchanged at 61% from the participation in 2015 (see Table 4.1.1).

Table 4.1.1 Overview of vaccination coverage for HPV vaccination in the Netherlands [266]

Reporting year	Birth cohort	% fully vaccinated against HPV
2011	1993-1996	52.3% mean*
2012	1997	56.0%
2013	1998	58.1%
2014	1999	58.9%
2015	2000	61.0%
2016	2001	61.0%

*1993: 49.0%,1994: 52.5%, 1995: 53.8%, 1996: 54.2%

4.2 Studies on determinants for vaccine uptake in girls in the Netherlands

In 2010, a multilevel study was performed between March and May 2009 to investigate determinants for HPV vaccine uptake (first dose for girls born between 1993 and 1996, catch-up vaccination campaign), as well as successful measures of implementation. Individual data (date of birth, country of birth, parents, postal code, distance between the girls' homes and the place of vaccination, vaccination status) could be extracted from the national vaccination register (Praeventis). In addition, detailed statistics on various background data were publicly available on the website of Statistics Netherlands (proportion of voters for the Reformed Political Party (SGP) and Christian Union (CU) at municipality level) and the Dutch Institute for Social Research (socioeconomic status (SES) at postal code level). Besides the collection of background data, a questionnaire was sent to all regional coordinators of the HPV vaccination campaigns at the child health services (CHS). The target population included 384,869 girls. A multilevel analysis showed that, at the individual level, younger and older girls were slightly less vaccinated and the number of previous doses of vaccine against MMR was a positive predictor for HPV immunization. Among the 22% of girls for whom their parents' country of birth was available, the highest uptake was observed when both parents were born in the Netherlands. The uptake was the lowest among girls with parents born in Turkey or Morocco. At the postal code level, higher uptake and areas with higher socio-economic status were correlated. At the municipality level, higher proportion of voters for SGP and CU at the last elections were associated with lower uptake. Results regarding implementation aspects showed that a shorter distance between home and vaccination centre was significantly associated with higher vaccine uptake, as well as organizing information meetings with pupils at school, working together with gynaecologists and a minimal use by CHSof local media (e.g. media focused on the experimental status of the vaccine), for which a dose-dependent effect could be observed [267].

In July 2009, a questionnaire study was conducted among the parents (93% female) of girls born in 1996 (vaccine acceptors (first dose) (N= 307, response rate 31%) vs vaccine decliners (N = 162, response rate 16%). Results from the multivariate analyses showed that the strongest determinants of not accepting HPV vaccination were: if the parents were religious, if they thought the information about the vaccine provided by the government was limited, if they had a low level of trust that the government would stop vaccinations if there were serious side effects and if they had concerns related to vaccine safety and the perceived effectiveness [268].

In addition, a study was performed on associated determinants for unvaccinated girls, dropout girls (girls who started, but did not complete the series of three vaccinations) and late adopters (girls who did not start with the vaccination initially, but started later on in the campaign). Some clear differences were found between unvaccinated and dropout girls in 2009, on the one hand, and the girls who were vaccinated according to the regular programme, on the other; i.e. more of them were born abroad, more of them lived in a big city and a relatively high

percentage of them had a low socio-economic status. Furthermore, relatively more unvaccinated girls live in areas with a higher proportion of voters that vote for religious political parties (i.e. SGP and CU) than girls were vaccinated according to the regular programme. Late adopters in 2009 also more often lived in a big city and had a low socio-economic status. Late adopters in 2010 and girls vaccinated according to the regular programme were more often born in the Netherlands, not living in a big city and more often did not have a low socio-economic status. [269]

Another study was performed where both 13/14-year-old girls born in 1995 or 1996 and their mothers were invited between November 2009 and January 2010 to fill in a questionnaire about determinants for future vaccination intention. Results among mothers (N= 952, 14% response rate) and their daughters (N = 642, 10% response rate) showed that, besides past HPV vaccination uptake, the social-psychological variables of attitude, beliefs about HPV vaccination, subjective norms and strength of habit were significantly associated with both the mothers' and the daughters' HPV vaccination intentions. The most dominant attitude-based beliefs were beliefs about the safety and relative effectiveness of the HPV vaccine, the belief that the vaccine would not be needed if the daughter was already sexually active and that the daughter was too young to receive the HPV vaccination, as well as a perceived economic profit for the pharmaceutical industry and trust in the government's policies with respect to prevention of infectious diseases. With regard to subjective norms, the influence of important others on the intent of HPV vaccination was most dominanted by close family members (mother, father and daughter). Social-psychological factors that were also related, but less consistently so, to HPV vaccination intention were the perception of the risk involved and anticipated regret. Daughters were more inclined to support vaccination if they perceived a higher susceptibility for cervical cancer without HPV vaccination (perceived severity was not taken into account). Mothers were more inclined to support vaccination if they anticipated more feelings of regret if their daughters received no vaccination and developed cervical cancer later in life. Mothers and daughters were more inclined to accept the HPV vaccination when they perceived it as an automatic event, without much thinking. Factors such as knowledge and past cancer experience did not play an important role. Almost all study participants knew someone from their close environment who has or has had cancer and the percentage of correct answers was also high [270].

Two questionnaire studies among parents (~93% female), one in June 2009 (before the decision to vaccinate or not) and one in November 2011 (after the second HPV vaccination), were performed with the aim of gaining insight into the determinants of vaccination uptake. The response rate of the baseline questionnaire was 29.8% (1762/5918) and a total of 1,067 respondents were willing to complete the follow-up questionnaire, 793 of which responded (74.3%). Hierarchical logistic regression analyses showed that uptake was predicted by a positive intention. Furthermore, parents who had postponed the decision had a higher uptake than parents who made the decision in 2010 (e.g. with passing ofhen time, passed there was less public debate and people were more reassured about the vaccine's safety and effectiveness).

Another determinant of vaccine uptake was anticipated regret if they chose not to vaccinate. A higher intention was associated with a positive attitude towards HPV vaccination, trust in the vaccine, anticipated regret if choosing not to vaccinate and social norms. Favourable changes in attitudes toward HPV uptake over time were significantly related to an increase in trust in the vaccine and the social norm over time and a decrease in ambivalence towards HPV vaccination [271].

A longitudinal study on determinants of HPV vaccination uptake in parents/guardians from different ethnic backgrounds in Amsterdam was performed by the Public Health Service of Amsterdam.
Parents/guardians of girls that were invited for HPV vaccination in 2014 were asked to complete a questionnaire on socio-demographics and the social-psychological determinants of HPV vaccination uptake in 2014. For this study, four ethnic groups were distinguished: Dutch (NL, n=723), Surinamese, Netherlands Antillean, and Aruban (SNA, n=126), Middle-Eastern and North-African (MENA, n=237) and Other (n=223). The MENA group was mainly composed of individuals with a Moroccan, Turkish or Egyptian background. In all ethnic groups, the intention to vaccinate was found to be the strongest predictor of the daughters' HPV vaccination uptake. The association between intention and uptake was strongest among the NL group and much lower in the other ethnic groups. Among the participants with a positive intention, the percentage who did not opt for vaccination was 4% in the NL group, 11% in the SNA group, 30% in the MENA group and 11% in the Other group. Among the participants with a negative intention, the percentage that did opt for vaccination was 11% in the NL group, 7% in the SNA group, 6% in the MENA group and 19% in the Other group. The intention to vaccinate was associated with determinants such as attitude, beliefs about the HPV vaccination, social norms and evaluation of the HPV information, but the determinants varied somewhat between the groups. For example, perceived susceptibility when choosing not to vaccinate was significantly associated with intention in the MENA group, but not in the other groups, and beliefs were not significantly associated in the MENA group, whereas this was the case in the other groups. The strength of association in the determinants of intention were largely similar across ethnic groups. The authors suggested that HPV vaccination campaigns could focus on the same determinants as were used for the Dutch group when targeting non-Dutch groups, though the mode of delivery of the intervention needs to be tailored to the different cultural backgrounds (by personal communication or via social media and, in their own language). Further research is needed to explain the observed discrepancy between intention and uptake, especially among parents/guardians in the non-Dutch groups [272].

In summary, the most important factors related to HPV intention/uptake were attitude towards HPV vaccination, beliefs about HPV vaccination (safety, relative effectiveness, trust in government's policies with respect to the prevention of infectious diseases), subjective and descriptive norms, strength of habit, and anticipated regret if choice was made not to vaccinate. The factors reported were more or less similar for parents (mothers) and their daughters and for girls at various ages. Furthermore, the same socio-psychological determinants were present among the vaccinated and non-vaccinated populations, for different

ethnicities, and the determinants stayed more or less the same before and after the introduction of HPV vaccination (personal communication Hilde van Keulen and Theo Paulussen, TNO-Leiden, the Netherlands). In addition, some studies also showed that orthodox reformed individuals, mothers born abroad and those with a lower socio-economic status had a lower vaccination coverage. Furthermore, it should be mentioned that the fact that not all studies showed the impact of demographic factors (or sometimes inconsistently so) might be due to the underrepresentation of some groups, such as persons with a lower educational level or migrants. Lastly, surprisingly we could not identify any Dutch studies about the attitude, knowledge and information needs of professionals (e.g. vaccination healthcare providers, gynaecologists and GPs) with regard to HPV vaccination.

4.3 Experience in other countries

4.3.1 Vaccine uptake among girls

In England, HPV immunization coverage for the priming dose in school year 8 (ages 2 and 13 years old) in 2015/16 was 87.0%, compared with 89.4% in 2014/15 [273]. Bruni et al. [274] have estimated that HPV vaccination coverage for various countries in the world, including countries in Europe. For example, for Austria the most recent estimated HPV vaccination coverage was 36% (cohort 2001), for France 20% (cohort 2003), for Belgium the HPV vaccination coverage lay in between 29% (Wallonia, cohort 2001) and 82% (Flanders, cohort 2002) and for Germany the estimated HPV coverage was 38% (cohort 2002). In Denmark the vaccination coverage for the first HPV dose dropped from 79% in 2014 (cohort 2002) to 23% in 2016 (cohort 2004; note: the vaccination coverage will probably increase due to a delay in registering vaccinations) (see Figure 4.3.1) after TV2, one of Denmark's national television stations, aired a documentary on March 26, 2015 about HPV vaccines entitled, "The Vaccinated Girls – Sick and Betrayed". It focused on the condition of 3 girls suffering from serious new medical conditions after being vaccinated against HPV with Gardasil [275].

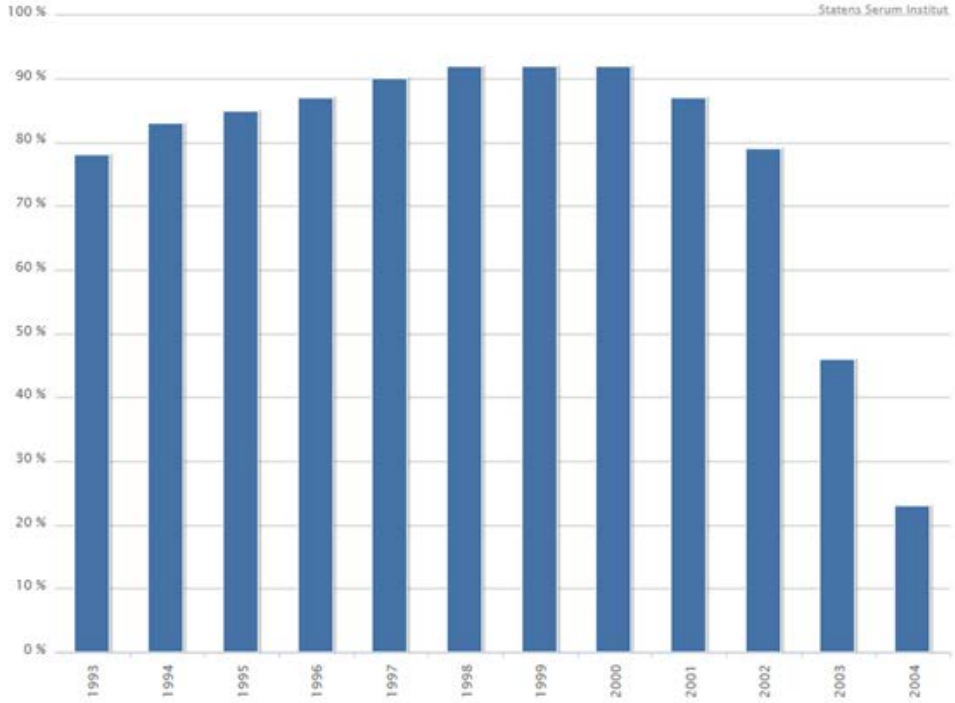

Figure 4.3.1 HPV vaccination coverage among girls in Denmark by birth cohort

Also in Ireland, they observed a decline in the number of girls receiving the 4vHPV vaccine. For 2015/2016, an uptake of 72.3% is provisionally reported. This represents a considerable drop from the 87% recorded during the 2014/2015 school year. The drop is probably due to a patient advocacy group representing over 350 young Irish women who state that they have developed long-term side effects following HPV vaccination. The significant drop in HPV vaccination rates suggests that parents and teenagers are concerned about the reported side effects (personal communication with Dr Brenda Corcoran from the National Immunisation Office in Ireland, [276, 277].

4.3.2 Vaccine uptake among boys

The following countries included HPV vaccination for boys: Australia, USA, Austria, regions in Italy and regions in Canada. When looking at the vaccination coverage in these countries, one should keep in mind the differences in publicly funded or whether they have to pay themselves. The organization around HPV vaccination can also differ. For example, in Canada on Prince Edward Island (PEI) there is a highly organized public health nursing programme that is involved in all childhood and school-based vaccinations. The vaccination coverage on PEI for boys was 79% for three doses (85% for girls) [278].
In Australia the HPV vaccine is provided for free at schools to all males and females aged 12-13 years under the National HPV Vaccination Program. The National HPV Vaccination Program began in 2007 for females, and was extended to include males in 2013. Here, the uptake (three doses) for males turning 15 in 2015 was between 59.0% and 71.3%, which was somewhat lower than for females (between 67.4% and 82.1%) [279].
In the USA, HPV vaccination coverage with ≥1 dose was 34.6% among boys and 57.3% for girls, and series completion (≥3 doses) was 13.9%

for boys and 37.6% for girls (2013). In the USA, the ACIP recommendation is in place and the cost of vaccination is borne by recipients and vaccination policies vary per state [280].

4.3.3 Factors associated with intention/uptake HPV vaccination in boys

Organizational factors known to increase HPV vaccination uptake were recommended by the vaccination healthcare provider [281], as was having various contacts/consults during the period one should be vaccinated (opportunities for asking questions and administering the vaccination) [282]. Related to this, lower vaccination coverage was observed in settings using a clinic-based delivery model (e.g. USA, Luxembourg), where the chance of missed opportunities or no show is higher, whereas in settings using a school-based delivery model higher coverage for HPV vaccination was observed (e.g. UK, Canada, Australia) as missed opportunities might be caught up the next school year [283]. From a questionnaire study (412 parents matched with their 412 sons (11-17 years)) conducted in 2015 in the USA, it was shown that both parents' and sons' vaccination willingness was associated with greater anticipated regret about the son contracting HPV if he did not get the vaccine, a greater perceived importance of protecting the son's future partner from HPV-related illness [281] and higher levels of a perceived likelihood of contracting HPV [281, 284, 285]. In addition, in the systematic review conducted by Radisic et al. [281] and the study done by Napolitano et al. [285], it was also found that the perceived benefits of vaccination (e.g. protecting their son from cancer and other diseases, including genital warts) was an important factor for vaccine acceptability. In the study conducted by Moss et al. [284], it was also shown that sons were less willing to be vaccinated if they had greater concerns about vaccination side effects in terms of pain, and parents were less likely to be willing to vaccinate if they thought their son would faint after vaccination. Another finding was that parents make decisions about HPV vaccination with minimal influence from their sons' beliefs, while sons' willingness reflects both their own and their parents' beliefs. Note that this might depend on the age of the son [284]. From an Italian study conducted among males aged 14-24 (N = 956), it was also shown that males who reported having their first vaginal sexual encounter after the age of 18 expressed a more positive attitude towards vaccination, since they might have a higher level of knowledge about the HPV infection [285]. Results from a questionnaire study conducted in 2016 among parents of males aged 8-18 years (N = 1381) in Canada showed that parents who had positive attitudes towards vaccination in general and the HPV vaccine in particular, who were influenced by important others (e.g. opinions of healthcare professionals, teachers and friends), who felt that the vaccine had limited influence on sexual behaviour (e.g. earlier sexual debut or higher number of sexual partners), and who had heard of HPV-associated disease were significantly more likely to report an intention to vaccinate boys against HPV [286]. In the systematic review conducted by Radisic et al. [281], other factors that negatively influenced vaccine acceptability were being uncertain about its effectiveness, having limited knowledge about HPV infection and vaccine availability, not having an older vaccinated daughter, not having frequent and open discussions between parents and son, and not having a commitment to equal rights for boys and girls and shared responsibility.

4.3.4 Expected differences between intention/uptake boys and girls

In the USA, one year after routine recommendation for males, coverage levels remained lower than they had been historically for females following licensure and recommendation. According to the authors, the difference might be due to the fact that the HPV vaccination of males is thought to be less necessary and/or due to differences in knowledge and attitudes among parents with regard to vaccinating girls or boys (e.g. unawareness of HPV recommendations, parents may perceive less risk of HPV infection for boys [287]) and the healthcare providers (HCPs) (e.g. 53% of USA paediatricians and family medicine physicians strongly recommended the HPV vaccine for females whereas only 14% strongly recommended it for males) [283]. In the Canadian study conducted by Ogilvie et al. [286], it was stated that parents who reported an intention to vaccinate their daughters were also highly likely to report an intention to vaccinate their sons. This was also shown in a systematic review conducted by Radisic et al. [281]. The studies above show that most socio-psychological factors were similar with respect to vaccine acceptability for girls and for boys, except the factor relating to protecting the son's future partner from HPV-related illness. Several studies showed that the parents of boys who attached greater importance to protecting the son's future partner from HPV-related illness also had a higher vaccine acceptability [281, 285].

4.4 Intention to accept vaccination among boys, males in the Netherlands

In a qualitative study, the factors influencing the HPV vaccination intentions of boys and their parents were explored. In total, seven focus group discussions (87 boys in total) were conducted with 12-year-old boys, in addition to interviews held with six parents of boys around this age, in order to assess the health beliefs, behavioural factors, communication preferences and information needs in regard to the HPV vaccination of boys. The majority of parents (5 out of 6) and boys had a positive attitude towards the HPV vaccine and intended to (let their sons) receive the vaccine. However, most of the participants had little knowledge about HPV and HPV vaccination, especially for boys. Parents and boys had a low-level perception of the risk of HPV infection and several participants were concerned about the side effects of the vaccine. Both parents and boys reported that parents would decide whether their sons would receive the vaccine or not. Most parents trusted the government to ensure that the vaccine was safe. Parents and boys would like to be informed about the HPV vaccination through a personal letter, via (several types of) (social) media and via information meetings held at schools or community health services [288].

4.5 Intention to accept vaccination among MSM and males visiting STI-clinics in the Netherlands

In March 2016, Soa Aids Nederland carried out qualitative research amongst young gay and bisexual men in the Netherlands about their knowledge of HPV, their attitudes towards HPV vaccination and their suggestions on ways to promote HPV vaccination amongst young gay and bisexual peers. MSM were selected for the interviews. Participants were interviewed either individually (n=16) or in small focus groups (n=6 per group). Prior to reading a fact sheet with key information on

HPV and HPV vaccination, the participants were asked what they already knew about HPV. After the fact sheet information was discussed, participants answered questions about their attitudes towards HPV vaccination. Finally, participants were asked what could be done to encourage HPV vaccination amongst gay and bisexual peers. In total, 28 adolescent MSM were interviewed, with an average age of 20 (range: 15–25 years). Their education level was above average (71% had higher education level). Half of the sample lived outside North Holland and Flevoland. Participants were unfamiliar with HPV and how HPV vaccination may offer protection against anogenital cancer and/or genital warts (depending on the vaccine). After reading the fact sheet, participants expressed low levels of willingness to receive vaccination. The current vaccine cost (over €300) was a major barrier for every participant. Respondents generally questioned the importance of HPV vaccination for themselves, primarily because of the perceived a low prevalence of HPV-related cancer versus the high rates of HPV infection; the current non-existence of free vaccination programmes for gay and bisexual men; and the lack of information and campaigns about HPV focused on gay and bisexual men. Sexually experienced boys wondered how effective the vaccine would be for them and participants who had a steady partner perceived a lower risk of becoming infected with HPV. In order to stimulate HPV vaccination uptake amongst (other) young gay and bisexual men, participants suggested the following: HPV vaccines should be offered for free, by default, to boys and girls and preferably via sexual health clinics; more attention should be given to HPV by providing information about HPV in schools and by promoting HPV vaccination via websites, social media and smartphone apps commonly used by young gay and bisexual men (K. Verwey, Soa Aids Nederland [210]).

In a study conducted by the Public Health Service in Amsterdam, the socio-psychological determinants of the intention to get vaccinated against HPV among male clients of the STI-clinic in Amsterdam were researched. From June to November 2015, men aged ≥18 years visiting the STI clinic were asked to complete a web-based questionnaire about their demographic background, the socio-psychological determinants of their HPV vaccination-related intentions and their sexual behaviour. The socio-psychological determinants of HPV vaccination that were included in the questionnaire were derived from the Theory of Planned Behaviour and Social Cognitive Theory. Additionally, the effect of different amounts of out-of-pocket payment (€50; €100; €200; €350) on their intention was explored. In total, 1,490 men participated; 1,053 (71%) were MSM. The median age was 33 years, inter-quartile range (IQR) 25–44. The median HPV knowledge score was 5 (IQR 4–6) out of a maximum of 7. HPV vaccination intention was high: mean of 1.7 [SD=1.4] in MSW and mean of 2.4 [SD=1.1] in MSM (on a scale of -3 to +3). In a multivariable analysis of the responses of MSW, the attitude towards HPV vaccination had the strongest association with HPV vaccination intention followed by self-efficacy. Additionally, anticipated regret and social influences were significantly associated with HPV vaccination intention. Among MSM, attitude and self-efficacy were also strongly associated with HPV vaccination intention. Anticipated regret, the number of friends that were expected to get vaccinated and outcome expectations were also associated with HPV vaccination intention.

Demographics and sexual behaviour variables did not have a large impact on intention. With each step increase in the required out-of-pocket payment for HPV vaccination, HPV vaccination intention decreased by a 0.81 (95% CI: 0.75–0.86) scale point on a scale of -3 to +3 among MSW and by 0.71 (95% CI: 0.67–0.75) among MSM (E. Marra, GGD Amsterdam [210]).

5 Health and economic impact of vaccination

Summary

A large number of economic evaluations regarding HPV vaccination in the Netherlands have been performed, consistently demonstrating the cost-effectiveness of HPV-16/18 vaccination for preadolescent girls. The current programme, reaching 61% of 12-year-old girls, is expected to lead to 48-56% fewer cervical cancer cases in the long run. The cost-effectiveness profile of girls' vaccination is further improved by the additional health gain from preventing non-cervical diseases, and through a reduced circulation of vaccine types HPV16/18. If vaccine uptake among 12-year-old girls continues at the achieved level of 61%, around 800 boys would need to be vaccinated to prevent one additional case of cancer in men. This figure assumes similar prophylactic VE against anogenital/oropharyngeal and against cervical infections, which remains to be demonstrated. Under this assumption, gender-neutral vaccination in the Dutch setting is highly likely to yield an incremental cost-effectiveness ratio below commonly accepted thresholds. The potential impact of targeted immunization for MSM is still uncertain, but an assessment for the UK suggests that the HPV vaccine might be offered cost-effectively to MSM up to age of 40.

5.1 Girls only; current situation in the Netherlands

Several analyses aimed at determining the cost-effectiveness of HPV vaccination in the Netherlands were conducted around the time of HPV vaccine introduction [289-292]. These studies assessed the direct benefit of vaccinating preadolescent girls with the aim of preventing cervical disease, incremental to the pre-existing cervical screening programme in the Netherlands. The indirect benefits of girls-only vaccination for non-vaccinated women and men were investigated later with transmission-dynamic models [36, 293, 294], initially with a focus on cervical disease prevention. Recent analyses have evaluated the extent to which the cost-effectiveness of girls-only HPV vaccination could be improved by the inclusion of non-cervical HPV-associated diseases [295-299].

5.1.1 Health gain cervical disease

Boot et al. [289] performed a first ballpark assessment of the potential impact of prophylactic HPV vaccines in the Netherlands. This study assumed that prophylactic HPV-16/18 vaccination could avoid 60% of cervical cancer cases, i.e. less than the 70-75% of cases attributable to HPV16/18 due to imperfect coverage and adherence at the introduction of HPV vaccination. This figure would correspond to 400 cervical cancer cases (107 of which were fatal) per vaccine-eligible cohort in the Netherlands. These suppositions were later confirmed with a Markov model that simulated the natural history of 14 oncogenic HPV types in relation to cervical disease. The model was calibrated to type-specific HPV prevalence and CIN2+ incidence in the Dutch cervical screening programme. Based on an 85% vaccine coverage and 95% efficacy against HPV16/18, Coupé et al. [290] predicted a decline, per cohort of 100 thousand women, from 634 lifetime cervical cancer cases (184 of

which fatal), under a scenario of screening only, to 247 cases (71 of which fatal) if cervical screening was complemented by HPV-16/18 vaccination for preadolescent girls. Partial cross-protection to HPV31/45 was assessed in sensitivity analyses: the relative reduction in cervical cancer incidence improved from 61% to 68% with 90% efficacy against these types. Rogoza et al. [292] assumed 50% cross-protective efficacy against HPV31 and 90% against HPV45, together with 95% efficacy against HPV16/18 in another Markov model calibrated to the Dutch setting. Under full vaccine coverage, HPV16/18 vaccination was predicted to yield a 57% reduction in CIN2+ cases and a 74% reduction in cervical cancer cases. Note that a reduction of 74% under full coverage corresponds to a reduction of 63% at 85% vaccine coverage, if herd effects are to be ignored. A cohort simulation study by De Kok et al. [291] yielded markedly different estimates for the impact of HPV-16/18 vaccination. Assuming 85% vaccine coverage and 70% efficacy against cervical cancer, the number of cervical cancer cases per cohort of 100,000 women was predicted to decline from 410 (170 of which fatal) to 170 (70 of which fatal) under scenarios of screening only and screening plus vaccination. Note that whilst the absolute number of cervical cancer cases to be prevented by HPV-16/18 vaccination is much lower than estimated in [290] and [292], the benefit in a relative sense is comparable, i.e. a 59% reduction in cervical cancer incidence in the absence of cross-protection. The low background incidence of cervical cancer under screening only was informed by a forward projection of a declining cervical cancer incidence until the end of the 21st century. However, subsequent analyses demonstrated that the per capita rate of cervical cancer incidence has increased since the beginning of this century [300].

The herd effects of HPV-16/18 vaccination have been studied by several groups in the Netherlands [36, 293, 294]. Bogaards et al. [36] developed an age-specific compartmental heterosexual transmission model that was fitted to type-specific HPV prevalence and clearance prior to the introduction of the HPV vaccine. Based on this model, an eventual 47% reduction in cervical cancer incidence was predicted for the whole population at a 50% vaccine-uptake among preadolescent girls. The lifetime risk of infection in non-vaccinated women was estimated to decline by 19.6% and 22.5% for HPV16 and -18, respectively. Whilst the risk of infection in non-vaccinated women further decreases with increasing vaccine uptake, the absolute number of indirectly averted cervical cancers cases was estimated to peak around an effective vaccine coverage of 60% at almost 70 cases per cohort of 100,000 women, which is between 20-25% of the overall number of cervical cancers prevented among vaccinated plus unvaccinated women. Matthijsse et al. [293] developed a stochastic microsimulation model for heterosexual HPV16 and -18 transmission that was fitted to pre-vaccine HPV16 and -18 prevalence data. The authors estimated that the current programme, reaching 60% of 12-year-old girls, will lead to HPV16 and -18 incidence reductions of between 64-75% and 58-73%, respectively, with the range reflecting uncertainty in the role of acquired immunity in HPV transmission models. This corresponds to 48-56% fewer cervical cancer cases in the long run. Note that the recently estimated figures are somewhat lower than predicted around the time of vaccine introduction, i.e. herd effects

do not fully compensate for the relatively low vaccine uptake in the Netherlands.

5.1.2 *Health gain non-cervical HPV-related diseases*

Boot et al. [289] already considered the potential impact of HPV-16/18 vaccination on female non-cervical cancers. Based on etiological evidence available at the time, it was suggested that HPV-16/18 vaccination could prevent 47 deaths per year in vaccinated women due to the prevention of vulvar, vaginal, anal and oral cavity cancers. For comparison, HPV-16/18 vaccination was expected to prevent 107 fatal cases of cervical cancer in their assessment. De Kok et al. [296] also considered oropharyngeal cancers in the impact of HPV-16/18 vaccination on non-cervical HPV-associated cancers. According to their estimates, the gain in life-years in vaccinated women would only be 21%, relative to the prevention of cervical cancer only. The relatively low contribution of non-cervical cancers to life-years gained is partly explained by the late occurrence of non-cervical cancers, compared with cervical cancers. Luttjeboer et al. [297] were the first to estimate the impact of the prophylactic HPV vaccine on non-cervical cancers by means of a Markov model. They predicted that between 20 and 35 cases of vulvar, vaginal, anal and oropharyngeal cancers combined could be prevented in each five-year age group between 50 and 90 years of age, under the assumption of full vaccine coverage and efficacy against persistent HPV-16/18 infection of 92.9%. Contrary to De Kok et al. [296], Luttjeboer et al. [297] considered the prevention of cancer cases by age, not solely mean age at cancer death, and included cross-protection for non-vaccine types HPV31/33/45/51 at 76.8%, 44.8%, 73.6% and 54.4%, respectively.

So far, Westra et al. [299] have provided the only model-based assessment of quadrivalent 4vHPV vaccine in the Netherlands. Using a Markov model that simulates the progression from HPV infection to cervical cancer or genital warts, it was predicted that 4,390 episodes of genital warts could be prevented in a cohort of 100,000 girls at a vaccine coverage of 50% against HPV6/11/16/18. This estimate did not include potential herd effects of reduced vaccine-type transmission.

Bogaards et al. [295] provided an estimate for the health gain in men derived from vaccinating girls against HPV16/18. At 60% vaccine coverage in preadolescent girls and 98% prophylactic efficacy against persistent HPV-16/18 infection (95% credible interval: 95-99%), an eventual 37% decrease in overall vaccine-preventable cancer burden in males was estimated. Reductions varied by anatomical site, as the male burden of oropharyngeal and especially anal HPV-related cancer is concentrated in MSM. The current girls-only vaccination programme was estimated to reduce the burden of HPV16/18-associated anal cancer by only 18%, of HPV16/18-associated oropharyngeal cancer by 46% and of HPV16/18-associated penile cancer by 54%.

5.1.3 *Cost-effectiveness*

The incremental cost-effectiveness ratio (ICER) of prophylactic HPV-16/18 vaccination relative to cervical screening was initially estimated at €24,000/QALY, assuming vaccination costs of €322/vaccinated girl [289], according to Dutch guidelines specifying annual discount rates of

4% for future costs and 1.5% for future health gains. This figure included anticipated savings from cervical disease prevention in the order of €9 million (undiscounted) per year. The duration of vaccine protection was largely unknown at the time and was identified as a major source of uncertainty. Using a Markov model for cervical disease progression from 14 oncogenic HPV types, Coupé et al. [290] estimated an ICER of €19,500/QALY in their base-case analysis at vaccination costs of €393/vaccinated girl. Scenarios of waning vaccine efficacy were explored in sensitivity analyses, strongly affecting the results. Rogoza et al. [292] estimated an ICER of €22,700/QALY at vaccination costs of €315/vaccinated girl and also established duration of vaccine protection as a major source of uncertainty. De Kok et al. [291] estimated an ICER of €19,700/QALY at vaccination costs of €404/vaccinated girl, when costs and health gains were discounted at 4% and 1.5%, respectively, per year. As before, the need for booster vaccinations resulting from waning vaccine protection negatively affected the ICER. Conversely, an increased efficacy for preventing cervical disease, e.g. resulting from cross-protection for non-vaccine types, had a considerable positive effect on the ICER. Using a transmission-dynamic model, Westra et al. [294] found the ICER of the existing HPV-16/18 vaccination programme with 60% coverage among preadolescent girls to be €9,500/QALY if cervical cancer prevention in both vaccinated and non-vaccinated women was taken into account. Westra et al. [299] also assessed the impact of genital warts in addition to cervical cancer prevention. Assuming a comparable willingness to pay for the prevention of genital warts and cancer, it was stated that the difference in ICERs between the bivalent and the quadrivalent vaccines could justify a slightly higher price (~7% per dose) in favour of the latter.

Including non-cervical HPV16/18-positive cancers in a health economic assessment of girls-only vaccination was predicted to lower the ICER of HPV-16/18 vaccination by between 10 and 31% in the Netherlands [296]. However, this estimate was derived from ad-hoc calculations, not from an explicit modelling study. Luttjeboer et al. [297] used a Markov model to simulate the impact of non-cervical cancer prevention on the ICER of girls-only vaccination and estimated an almost 40% reduction in the ICER of HPV-16/18 vaccination. Including cross-protection for non-vaccine types resulted in an additional 19% reduction in the ICER. Luttjeboer et al. [297] calculated an ICER of €5,815/QALY at vaccination costs of €360/vaccinated girl and suggested that vaccinating girls with the bivalent vaccine might become cost-saving at vaccine prices realized after tendering, i.e. at dose prices below €60. Suijkerbuijk et al. [298] recently performed a systematic review of the health economic literature to estimate the impact of non-cervical cancer prevention on the cost-effectiveness of prophylactic HPV vaccination. Inclusion of non-cervical HPV-associated diseases led to a mean decrease in the ICER of girls-only vaccination, relative to cervical screening, by a factor of 2.85 (95% CI 1.35–4.36) in within-study comparisons. This figure is substantially larger than the reductions predicted by [296] and [297], presumably because of herd effects in non-vaccinated women and men. Qendri et al. [301] re-assessed the cost-effectiveness of the current vaccination programme in the Netherlands, taking into account all herd effects due to reduced heterosexual HPV-16/18 transmission, and estimated a

twofold reduction in the ICER when including non-cervical cancers in a health economic assessment of girls-only vaccination.

5.2 Gender neutral; including boys in addition to girls

5.2.1 HPV-related disease burden in men

De Kok et al. [296] have calculated that 422 life-years may be gained per cohort of 100,000 men by the elimination of HPV16/18-associated penile, anal, oropharyngeal and oral cavity cancers. This constitutes 12.5% of the potential health gain from the elimination of all HPV16/18-associated cancers in women in their analysis. Bogaards et al. [295] estimated that 1,490 quality-adjusted life-years might be gained per 100 thousand men by the elimination of HPV16/18-associated penile, anal and oropharyngeal cancers. When expressing health gain in life-years, Bogaards et al. [295] still provide an over threefold higher estimate than De Kok et al. [296]. This discrepancy is largely explained by the fourfold higher lifetime incidence of oropharyngeal cancer in men (i.e. 305 vs 78 per 100 thousand men) and less optimistic cancer survival rates in [295] as compared with [296]. Bogaards et al. [295] based their analyses on recently updated data from the Dutch cancer registry, with explicit mention of oropharynx cancer incidence, whereas De Kok et al. [296] made conservative assumptions regarding the proportion of oropharynx among total pharynx cancer cases. In addition, Bogaards et al. [295] accounted for the significant increase in HPV positivity rates in oropharyngeal cancer specimens since 1990 [97]. Trend analyses have revealed a steadily increasing proportion of males in the overall HPV-related cancer burden in the Netherlands over the past 25 years, with the highest increase due to oropharyngeal cancer. Over the period 2011-2014, HPV16/18-positive cancers of the oropharynx were estimated to account for approximately 50% of the total male HPV-related disease burden [302]. The male share of the overall burden of HPV-associated diseases in the Netherlands in 2014 was estimated at 25%.

5.2.2 Relative effectiveness of including boys vs increasing uptake in girls

Bogaards et al. [303] considered the efficiency of vaccinating boys relative to increasing the vaccine uptake among girls in preadolescent HPV vaccination programmes. Using a range of mathematical models, they concluded that increasing vaccine uptake among girls is more effective in reducing HPV prevalence throughout the heterosexual population, in terms of incremental gains per vaccine dose administered, than including boys in existing vaccination programmes. This prediction has been confirmed repeatedly, notably in a comparative study of sixteen different transmission-dynamic models from various high-income countries [304]. Matthijsse et al. [294] have estimated that vaccinating boys at an equal rate as girls, i.e. 60% uptake in 12-year-olds, would reduce HPV16 and HPV18 incidence among heterosexuals by 79-89% and 84-98%, respectively, relative to pre-vaccine levels. Note that complete coverage of 12-year-old girls would be sufficient to eliminate heterosexual transmission of HPV16 and HPV18.

5.2.3 *Cost-effectiveness of boys' vaccination under achieved vs increased girls' uptake*

If the uptake of the HPV vaccine among 12-year-old girls continues at the achieved level of around 60%, approximately 800 boys would need to be vaccinated to prevent one additional case of cancer in men [295]. This figure takes into account the indirect protection of men from the girls-only vaccination programme, but does not consider additional herd effects from vaccinating boys. If vaccine uptake in girls were to increase to 90%, over 1,700 boys would need to be vaccinated to prevent an additional case of cancer in men. For comparison, at HPV vaccine introduction it was calculated that around 200 women would need to be vaccinated to prevent one case of cervical cancer [1]. Initial results of a formal cost-effectiveness analysis, taking into account the decline in vaccine costs due to reduced dosing schedules and tender negotiations in the Netherlands [305], suggest that a gender-neutral vaccination programme in the Dutch setting is highly likely to yield an ICER below commonly accepted willingness-to-pay thresholds [301].

5.3 Adult vaccination

5.3.1 *Women only*

In light of the relatively young sexual debut of teenage women in the Netherlands, Boot et al. [289] questioned the need and extent of a catch-up vaccination programme for young women. At the HPV vaccine introduction in the Netherlands, the upper age of the catch-up programme was pragmatically set at sixteen years, the median age of sexual debut [1]. Bogaards et al. [306] used a transmission model to estimate the clinical benefit and cost-effectiveness of vaccinating women aged 17-25 years in 2010, correcting for indirect protection from vaccination of younger birth cohorts. In the base-case analysis, full protection to HPV-16/18 infection was assumed if no prior exposure to those types had occurred. Sensitivity analyses investigated the effect of (partial) cross-protection on non-vaccine types; and the efficacy for subsequent infections, irrespective of infection status at the time of vaccination. The ICER for vaccinating all 17 to 25-year-old women was €22,526/QALY at a vaccine price of €65/dose and 4%-1.5% discounting for cost and health gains. If cross-protection against HPV31/33/45/58 was included, the ICER dropped to €14,734/QALY. Westra et al. [307] performed a similar analysis based on a Markov model that did not consider herd effects or acquired immunity from prior exposure to HPV16/18. At a vaccine price of €105/dose, and ignoring cross-protection for non-vaccine types, they calculated an average ICER of €26,900/QALY for a catch-up programme including all women between 12 and 25 years old. Cohort-specific ICERs remained below €30,000/QALY up to the age of 23.

5.3.2 *Men and women*

Matthijsse et al. [308] evaluated the public health benefits of routine HPV vaccination for adult men and women in the Netherlands, using a stochastic microsimulation model for HPV-16/18 transmission in the Netherlands. The authors investigated the impact of a one-time mass campaign conducted among women and (optionally) men aged 25-45 in 2016; they also investigated the impact of the routine vaccination of previously non-vaccinated women at age 30 at the first round of cervical

screening from 2016 onwards; and they investigated the impact of vaccinating previously non-vaccinated women and (optionally) men aged 15-29 at STI clinics from 2016 onwards. For the one-time mass campaign, the authors assumed that uptake rates in women and men would be similar to the age-specific attendance of cervical screening. In other strategies, an uptake of 100% was assumed. Strategies targeting both men and women were evaluated conditional on a gender-neutral preadolescent vaccination programme. A combined strategy of vaccinating all vaccine-naïve 15 to 29-year-old STI clinic visitors and 30-year-old women at their first cervical screening visit was found to have the largest impact, reducing HPV16 and -18 incidence by 63% and 84% relative to the current vaccination programme.

5.3.3 Men who have sex with men

The potential impact of targeted HPV immunization on MSM is still uncertain, partly due to a scarcity of data on the epidemiology of HPV in MSM as compared with women; and its impact on vaccine efficacy against relevant diseases in previously exposed populations is also unclear. The first health economic assessment of targeted vaccination of MSM has recently been published. Ong et al. [309] converted an existing model for heterosexual transmission to resemble transmission of HPV6/11/16/18 among MSM in the UK, using Natsal-3 data on sexual behaviour. The model was fitted to prevalence of anal HPV infections among 511 MSM. The authors modelled strategies of offering HPV vaccine to either HIV-positive or all MSM visiting genito-urinary medicine clinics, from ages 16 up to 40. The incidence of anal cancer was predicted to decline by 56% if all clinic-visiting MSM up to the age of 40 were offered vaccination, which would constitute a cost-effective intervention at a vaccine dose price of £48. Offering HPV vaccine to HIV-positive MSM remained cost-effective in all sensitivity analyses performed. Bogaards et al. developed a novel transmission model for penile-anal HPV-16 transmission that was informed by sexual behaviour data from the H2M study and fitted to longitudinal data on anal and penile HPV-16 infection among 456 HIV-negative MSM. Assuming a 65% efficacy on the hazard of HPV-16 infections and the ITT efficacy reported against external anogenital lesions in 16 to 26-year-old MSM with previous exposure [139], the authors estimated a 42% reduction in anogenital HPV-16 prevalence if 50% of MSM could be reached by age 26. Such a reduction would translate into an eventual prevention of 30 anal and penile cancer cases per year. Note that these predictions have not yet been published in a peer-reviewed journal.

6 List of abbreviations

AAHS	amorphous aluminum hydroxyphosphate sulphate adjuvant
Aca	anal carcinoma
ACIP	Advisory Committee on Immunization Practices
AE	adverse event
AEFI	adverse event following immunization
AGW	anogenital warts
AIN	anal intraepithelial neoplasia
AIS	adenocarcinoma in situ
aOR	adjusted odds ratio
AS04	adjuvant system 04 (aluminum hydroxyl and monophosphoryl lipid A)
ASC-H	atypical squamous cells, cannot rule out high-grade squamous intraepithelial lesions
ASC-US	atypical squamous cells of undetermined significance
ATP	according-to-protocol
CBS	Statistics Netherlands
CBO	Dutch Institute for Healthcare Improvement
CHMP	Committee for Medical Products for Human Use
CHS	child health services
CI	confidence interval
CIb	Centre for Infection Disease Control
CIN	cervical intraepithelial lesions
CrI	credible interval
CRPS	complex regional pain syndrome
CSI study	Chlamydia Screening and Intervention study
CU	Christian Union
CVS	cervical secretion
CVT	Costa Rica Vaccine Trial
CxCa	cervix carcinoma
DALY	disability-adjusted life-year
DNA	desoxyribonucleic acid
E	functional coding region coding for early viral function
EGL	external genital lesions
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EPAR	European public assessments reports
EU	European Union
FDA	Food and Drug Administration
GMC	geometric mean concentrations
GMT	geometric mean titres
GP	general practitioner
GST-L1-MIA	glutathione S-transferase L1-based Multiplex immunoassay
GW	genital warts
HAV	hepatitis A virus
HAVANA	HPV Among Vaccinated and Non-vaccinated Adolescents

HBV	hepatitis B virus
HCPs	healthcare providers
HG-CIN	high-grade cervical lesions
HIV	human immunodeficiency virus
HPV	human papillomavirus
HPV2D	study to monitor the two-dose vaccination schedule
hr	high-risk
H2M study	HPV and HIV in MSM study
ICER	incremental cost-effectiveness ratio
IQR	inter-quartile range
IRR	incidence rate ratio
ITT	intention-to-treat
IU/ml	international units per millilitre
JIA	juvenile idiopathic arthritis
JMD	Juvenile Dermatomyositis
L	functional coding region of late viral function
LCR	long control region
LIA	Luminex immunoassay
lr	low-risk
mcg	microgram
MENA	people from the Middle East and North Africa
MMR	combination of measles, mumps and rubella vaccines
mMU/ml	milli-Merck units per millilitre
MSM	men who have sex with men
MSW	men who have sex only with women
NA	not applicable
NIP	National Immunisation Programme
NIVEL	Netherlands Institute for Health Services Research
NL	people from the Netherlands
NOADs	new onset autoimmune diseases
OPSCC	oropharyngeal squamous cell carcinomas
OR	odds ratio
ORF	open reading frame
PAFs	population-attributable fractions
PAP test	the Papanicolaou test
PASSYON study	Papillomavirus Surveillance among STI clinic Youngsters in the Netherlands
PATRICIA	Papilloma TrIal against Cancer In young Adults
PBNA	pseudovirion-based neutralisation assay
PCR	polymerase chain reaction
PEI	Prince Edward Island
PIENTER study	study assessing immunisation effect to evaluate the NIP
PIN	penile/perineal/perianal intraepithelial neoplasia
PM	person-months
POTS	postal orthostatic tachycardia syndrome
PP	per-protocol
PR	prevalence ratio
PRAC	Pharmacovigilance Risk Assessment Committee
PSURs	periodic safety update reports
PV	Papillomaviridae
PY	person-years
QALY	quality-adjusted life year

RIVM	National Institute for Public Health and the Environment, the Netherlands
RNA	ribonucleic acid
RR	relative risk
RRP	recurrent respiratory papillomatosis
SAE	serious adverse event
SES	socio-economic status
SGP	Reformed Political Party
SLE	systemic lupus erythematosus
	SNA people from Suriname, Netherlands Antilles and Aruba
SPC	Summary of Product Characteristics
STI clinic	sexually transmitted infections
TVC	total vaccinated cohort
TVCE	total vaccinated cohort for efficacy
	TVC-naïve women DNA-negative for all HPV types tested at baseline
VaCa	vaginal carcinoma
VaIN	vaginal intraepithelial neoplasia
VE	vaccine efficacy
VIN	vulvar intraepithelial neoplasia
VIVIANE	Vaccine Immunogenicity And Efficacy
VLP	virus-like-particle
	VLP-ELISA virus-like-particle enzyme-linked immunosorbent assay
VTE	venous thromboembolism
VuCa	vulvar carcinoma
VUmc	VU University Medical Center Amsterdam
YLD	years lived with disability
YLL	years of life lost
2vHPV	bivalent HPV vaccine
4vHPV	quadrivalent HPV vaccine
9vHPV	nonavalent HPV vaccine

7 Literature

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Appendix A

Description of analysis populations of the different trials

2vHPV:
HPV-001/007/023, Patricia, CVT-trial, Viviane [120, 121]
Panel 1 describes the inclusion criteria for the cohorts. Some women were excluded from some analyses, e.g. analyses of women without evidence of previous infection excluded women who were seropositive and/or DNA-positive at baseline. The inclusion criteria for the primary analyses of each study are shown in Panel 2.
ATP: according-to-protocol; TVC: total vaccinated cohort; TVC-E: total vaccinated cohort for efficacy; TVC-naïve: women DNA-negative for all HPV types tested at baseline.

Panel 1

Criteria	ATP	TVC-E	TVC	TVC-naïve
Cytology at baseline	Negative or low-grade	Negative or low-grade	Irrespective ≥1	Negative ≥1
Number of vaccine doses received	3	≥1		
Case counting beginning (say after)	Third vaccination	First vaccination	First vaccination	First vaccination
Study and procedures[a]	Met eligibility criteria and complied with protocol	No requirement	No requirement	No requirement

[a] For all cohorts, data had to be available for efficacy endpoints, i.e. baseline PCR or cytology sample and one further sample.
ATP = according-to-protocol; TVC = total vaccinated cohort; TVCE = total vaccinated cohort for efficacy.

Panel 2

Study	Endpoint: HPV DNA associated with infection or abnormality	Women in analysis: HPV DNA status for 14 oncogenic HPV types[a] and serostatus for HPV 16 18[b] for corresponding HPV type at baseline and during vaccination course					
		ATP	TVC-E	TVC[f]	TVC-naïve[f]	TVC-previously exposed[f]	TVC- currently exposed[f]
HPV-001/007/023 [120, 121]	HPV-16/18	DNA-negative M0 and M6 for analysed type[b]		DNA-negative for 14 types and sero-negative per enrollment criteria[c]			
Patricia [120, 121]	HPV-16/18	DNA-negative M0 and M6, seronegative M0 for analysed type	DNA negative and seronegative at M0 for analysed type		DNA-negative for 14 types M0, seronegative for HPV 16 and HPV18 M0[d]		
CVT-trial [120, 121]	HPV-16/18	DNA-negative M0 and M6 for analysed type		Irrespective of HPV	DNA-negative for 14 types M0, seronegative for HPV 16 and HPV18 M0[d,e] and did not receive cervical exision treatment (LEEP) during vaccination phase.	DNA-negative for 14 types M0, seropositive for HPV 16 and HPV18 M0[d]	
CVT-trial (Beachler) [40]	HPV-16/18			All women who consented to cervical, anal and oral samples at the 4 year CVT visit and had HPV DNA test results available.	DNA-negative for 14 types M0, seronegative for HPV 16 and HPV18 M0 and did not receive cervical exision treatment (LEEP) during vaccination phase.	DNA-negative for HPV16/18 and seropositive for HPV16 and HPV18	DNA-positive for HPV16/18 regardless of serologic status

Study	Endpoint: HPV DNA associated with infection or abnormality	Women in analysis: HPV DNA status for 14 oncogenic HPV types[a] and serostatus for HPV 16 18[b] for corresponding HPV type at baseline and during vaccination course					
		ATP	TVC-E	TVC[f]	TVC-naïve[f]	TVC-previously exposed[f]	TVC- currently exposed[f]
CVT-trial (Kreimer) [132]	HPV-16/18			All women who consented to anal samples and HPV results available.	DNA-negative and seronegative for HPV-16 and -18. Not biopsied for CIN or treated with LEEP. Participants should have received three-doses.		
CVT-trial (Herrero) **[145]**	HPV-16/18		DNA-negative and seronegative at M0 for analysed type				
Viviane [120]	HPV-16/18	DNA-negative M0 and M6, stratified for serostatus at M0 for analysed type		Irrespective of HPV DNA or serostatus	Cervical HPV16/18 DNA-negative or seronegative for HPV16/18		

[a] The 14 oncogenic HPV types analysed are 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
[b] Serostatus determined for HPV16 and HPV18 only
[c] The HPV-001/007/023 study enrolled only women who were seronegative for HPV16/18 and HPV DNA-negative for 14 oncogenic HPV types
[d] As defined by cohort criteria
[e] As PATRICIA
[f] The TVC is called full cohort in the manuscript of Beachler et al. and Kreimer et al. Kreimer et al, called the naïve cohort restricted.
ATP: according-to-protocol; M0: Month 0; M6: Month 6; TVC: total vaccinated cohort; TVC-E: total vaccinated cohort for efficacy; TVC-naïve: women DNA-negative for all HPV types tested at baseline.

2vHPV and 4vHPV (meta-analysis; Deleré et al, 2014)[126]:
HPV-negative = Women who were negative for HPV 16 or HPV18 at baseline or who were not yet sexually active.

4vHPV:
FUTURE I/II and Villa et al. 2005 [134, 137]

Details of different analysis populations analysed for efficacy of 4vHPV vaccine within the FUTURE I/II studies

Criteria	ATP	PP	TVC-naïve	Intention to treat	Modified ITT
Number of vaccine doses received	3	3	≥1	≥1	≥1
Analysis population	DNA-negative and seronegative for HPV 6, 11, 16, 18 M0 and M7	DNA-negative and seronegative for HPV 6, 11, 16, 18 M0 and M7	DNA-negative for 14 types M0, seronegative for HPV 6, 11, 16 and HPV18 M0, and a negative cervical smear test M0[a]	Irrespective of HPV DNA or serostatus	HPV DNA-negative or seronegative to the relevant HPV type at enrolment
Case counting beginning (say after)	Third vaccination	Third vaccination	First vaccination	First vaccination	First vaccination
Study and procedures	Met eligibility criteria and complied with protocol	Met eligibility criteria and complied with protocol	No requirement	No requirement	No requirement
Endpoint related to	HPV 6,11,16,18	HPV 6,11,16,18	HPV 6,11,16,18	HPV 6,11,16,18 and any HPV type	HPV 6,11,16,18 and any HPV type

[a] The 14 oncogenic HPV types analysed are 6, 11 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59
ATP = according-to-protocol; ITT = intention-to-treat; TVC = total vaccinated cohort; PP = per-protocol.

Protocol 020

Criteria	PP	PP-Naïve	Intention to treat
Number of vaccine doses received	3	3	≥1
Analysis population	DNA-negative and seronegative for HPV 6, 11, 16, 18 M0 and M7	DNA-negative for 14 types M0, seronegative for HPV 6, 11, 16 and HPV18 M0	Irrespective of HPV DNA or serostatus

PP = per-protocol.

9vHPV (Joura, 2015)[125]:
PP = Participants who received all three doses of vaccine within 1 year, did not have the HPV type being analysed (i.e. were seronegative on day 1 and PCR-negative from day 1 through month 7) and had no protocol violations.

Erratum

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Correction:
Table 2.1.1:
The quadrivalent vaccine and the nonavalent vaccine are mentioned to be registered for the ages 9-26 years. However, both vaccines are registered for the use in persons from the age of 9 years and have no upper limit. For the dose schedule this means that a two-dose schedule is indicated for 9-14-year-olds and the three-dose schedule for the ages 15 years and older.

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