HPV in minority populations

Epidemiology and vaccination acceptability

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CHAPTER 1

Introduction
HUMAN PAPILLOMAVIRUS

Papillomaviruses are thought to have evolved with their hosts for over 300 million years and have likely evolved with humans from the start of our evolutionary history [1]. Despite this intimate connection between humans and papillomaviruses, it was not until the late 1970s that the impact of papillomaviruses on human health was acknowledged by establishing the first link between human papillomavirus (HPV) and cervical cancer [2,3]. This landmark finding resulted in an avalanche of HPV related research that unfolded over the next decades and now provides a panoramic view on the implications of HPV infections in humans. Currently, over 150 papillomavirus types infecting humans have been identified. These types can be clustered into five genera (alpha, beta, gamma, nu, mu HPV) occupying different niches of the human body [4]. Of particular interest are the alpha-types, which infect cutaneous and mucosal epithelium. The alpha-types that infect cutaneous epithelium, are associated with (flat) warts and have until now not been associated with cancer [4]. Alpha HPV types infecting the mucosal tissue on the other hand, can be carcinogenic and are subdivided into three different main groups depending on whether they are carcinogenic at the cervix. Group 1 (high-risk HPV types) includes types that have been shown to cause squamous cell carcinoma (SCC) and adenocarcinoma (AD) of the cervix. Group 2 are types that are probably or possibly carcinogenic and comprises types which are possibly carcinogenic based on epidemiological data, their close phylogenetic relationship with other HPV types classified as high-risk, and because of its probable similarity in their mechanism of infection. Group 3 (low-risk HPV types) includes types causing genital warts [4,5]. Further research on the beta and gamma genera infecting cutaneous tissue is necessary as knowledge on their carcinogenic potential is very limited. Based on the limited data available they are now all classified into group 3 with exception of HPV-5 and HPV-8 which are classified into group 2 based on their ‘probably carcinogenic’ character in patients with epidermodysplasia verruciformis (an inherited skin disorder known as the “tree man illness”) [4,5]. Although the classification of HPV types is based on the carcinogenic character at the cervix, it is well known that high-risk HPV types also cause cancer at other sites. High-risk HPV types have been found to cause (i) nearly all cervical cancers, (ii) a large proportion of other anogenital cancers including cancers of the penis in men, of the vagina and vulva in women, and of the anus in both men and women, and, (iii) a growing proportion of head and neck cancers in both men and women (at the tonsils, oropharynx, and base of tongue) [6–8]. Within the high-risk types, HPV-16 and HPV-18 have been found to cause the largest fraction of all HPV related cancers [6,9,10], while within the low-risk HPV types HPV-6 and HPV-11 cause about 90% of genital warts [4]. In this thesis we focus on the high-risk HPV types infecting men and women.
HPV is a sexually transmitted infection [11,12], and women have a remarkable 30-50% risk to get infected with HPV during their first years of sexual activity [13] (Figure 1, step 1). Among women the risk to get infected is highest in the first years of sexual activity and declines with age [14] while among men the infection risk remains approximately constant across the entire life span [15].

For an HPV to infect the basal layer, a micro wound, hair follicle, or columnar stratified junction (at the cervix or anal canal) is an essential point of entry [4]. It is estimated that eventually 80% of all sexually active individuals will have an HPV infection during her or his life [16]. Of these infections, almost 90% are cleared within two years in both men and women [15,17,18] (Figure 1, step 1). HPV clearance, however, is a complex process that depends on a multitude of factors. High-risk HPV types for instance, typically require a longer time to clear than low-risk HPV types [19,20], and it has been found that HPV-16 clears slower than the other high-risk types [4,20]. Furthermore, previous studies have shown that African-American women take almost twice as long to clear an HPV infection when compared to European American women [21], suggesting that ethnic background may also play a role. Immunosuppression is another important risk factor, especially HIV status, as slower

![Figure 1. Natural history of HPV and HPV related cancer in humans. Major steps in the carcinogenesis of HPV related cancer. Figure is based on published schematic representations of natural history [10,17,24]. Abbreviations: HPV DNA - = HPV DNA negative, HPV DNA + = HPV DNA positive, HPV sero - = HPV seronegative (antibodies not present), HPV sero + = HPV seropositive (antibodies present).]
clearances time have been observed for anal and cervical HPV infection among HIV-positive individuals when compared to HIV-negative individuals [22,23].

Interestingly, not everyone with an HPV infection will develop antibodies against HPV (Figure 1, step 2). Only a relatively small proportion of HPV DNA positive men (~20%) [25] and a larger proportion of HPV DNA positive women (~60%) [26] develop antibodies (i.e. become HPV seropositive) against an HPV infection within 13-24 months. As a consequence, higher HPV seroprevalences are typically found among women than men [27–29]. The site of infection (oral, anal, vaginal/cervical, or penile) and the duration of this infection may affect the probability of seroconversion. Furthermore, lower HPV seroprevalence is observed among older women. This may be caused by waning of antibodies, decrease in exposure, or a cohort effect (e.g. lower sexual risk behavior in older cohorts) (Figure 1, step 3) [29,30]. Previous studies have indicated that such naturally acquired HPV antibodies may provide modest protection against subsequent type-specific infections in women but not in men [31].

As mentioned above, almost 90% of HPV infections eventually get cleared, leaving the remaining ~10% of infections to persist within a cell [15,17,18] – an event with possibly dramatic consequences. The road from the initial HPV infection of a cell to full blown cancer is long, giving the body a window of opportunity (10-20 years in the case of cervical cancer) to backtrack on the path taken by that renegade cell [32]. After the initial infection of a human cell by HPV, mild abnormalities may be observed (Figure 1, e.g. cervical intraepithelial neoplasia 1 [CIN1]; anal intraepithelial neoplasia [AIN1]). Yet when an HPV infection becomes persistent, this mild abnormality develops into a true cancer precursor in 3-5% of cases (e.g. CIN2 and CIN3; AIN2 and AIN3) [10,17,24]. Among women, 30%-40% of untreated CIN2/CIN3 will eventually develop into invasive cervical cancer (Figure 1) [10]. Not a lot is known on the progression of AIN to anal cancer are currently available [33].

Recent data show that cervical cancer is the 4th most common cancer worldwide (527,624 new cases and 265,672 deaths in 2012) [9]. Of all HPV attributable cancers worldwide 87% are cervical cancers while the remaining 13% are cancers of (in decreasing order) the anus, oropharynx, vulva, penis, and vagina [34]. The burden of cervical cancer is not equally distributed around the globe with a staggering 5-6 times higher incidence and mortality in sub-Saharan Africa, Southern Asia, and South America when compared to Northern America, Australia/New Zealand, and Western Europe [9,34]. There is also high heterogeneity within regions, between countries, by age, and by risk group [9,34,35]. For example, in the Netherlands a study on the incidence of cervical cancer diagnosed between 1996-2009 showed that women from ethnic minorities have a higher risk to be diagnosed with cervical cancer when compared to native Dutch women, with the highest risk for Surinamese women, followed by Moroccan, Antillean/Aruban, and Turkish women (standardized incidence ratio
[SIR] ranging between 1.8 (95% CI 1.6–2.2) for Surinamese and 1.2 (0.9–1.5) for Turkish women when compared to Dutch native women) [36].

Data on HPV related cancers other than the cervix is growing but still limited [9], possibly because of their relative rarity. Anal and head and neck cancer have gained interest in the past couple of years [9]. Anal cancer in the general population is rare, with higher incidences among women than among men [9]. Yet men who have sex with men (MSM), and particularly HIV-positive MSM, have high incidences, up to 78/100,000 person-years among HIV-positive MSM living in the combination antiretroviral therapy-era (cART-era; from 1996 onwards) [33]. A large proportion of head and neck cancers is attributable to tobacco and alcohol use [9], however, as tobacco and alcohol use are decreasing in several Western countries, HPV infections may become responsible for a larger fraction of those cancers [20,35]. Furthermore, a rise in head and neck cancer has been observed overall over the world. In North-America, Sweden, and Australia these increases were most pronounced in younger birth cohorts, suggesting that higher sexual risk behavior in these cohorts may have led to an increase in the proportion of cancers attributable to HPV [35].

HUMAN PAPILLOMAVIRUS – RISK FACTORS

It is hard to disentangle risk factors for HPV infection, HPV seropositivity, and HPV cancer (whether prevalence, incidence, persistence, or clearance). Risk factors for infection, seropositivity, and cancer typically go hand in hand, but in epidemiology these outcomes are often presented as separate entities. The effect of risk factors (Figure 1, block A) varies according to which body site is affected. A main reason to investigate these risk factors is that despite HPV being necessary for the development of (cervical) cancer, it is not sufficient - with each individual having his/her own causal pie [37].

The debate on whether or not HPV is a sexually transmitted virus has been closed long ago and it is now well established that sexual risk behavior is one of the main risk factors for anogenital HPV infection and, ultimately, for cancer [11,12,30,38–42]. Other factors shown to be conducive to progression to cancer are smoking, long-term hormonal contraceptive use, and HIV infection [8,9]. However, the increased HPV-related cancer incidence among HIV-positive individuals remains to be elucidated as limited data from longitudinal studies are available. Factors that may contribute to the higher burden of HPV-related cancer among HIV-positive individuals are hypothesized to be higher exposure to HPV, slower clearance rate of HPV infections, a higher transition rate from a persistent HPV infection to (pre-)cancer, or behavioral factors (e.g. smoking) [43,44]. HIV-positive MSM from the pre-cART-era show lower incidences of anal cancer than HIV-positive MSM from the cART-era
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This phenomenon may be due to the longer survival of individuals from the cART-era due to which these individuals with a persistent HPV infection have more time to develop HPV-related cancer. The interaction of HPV with other sexually transmitted infections (like *Chlamydia trachomatis* and herpes simplex virus type-2) is still under debate. Host factors including genetic factors and factors related to the immune response, and viral factors are also hypothesized to play an important, yet currently ill-understood, role [8,9].

**HPV PREVENTION**

HPV induced cancers can be prevented in three ways. Primary prevention refers to the prevention of infection before it occurs. Due to the very high transmission rate of HPV, vaccination against HPV infection seems to be the only feasible method of primary prevention (perhaps in addition to complete sexual abstinence, which may not be a viable option for many). Secondary prevention involves screening for HPV-induced precancerous stages before an actual cancer has developed; when pre-cancer is diagnosed, this is treated. Tertiary prevention refers to the treatment of women with cervical cancer (Figure 1). Below we describe the methods and protocols used for primary and secondary prevention within the Dutch setting.

**HPV vaccines**

Currently there are three types of prophylactic vaccines approved for women by the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA): a bivalent vaccine that primarily protects against HPV-16 and HPV-18 (Cervarix, approved by the EMA in 2007 [45] and the FDA in 2009 [46]), a quadrivalent vaccine that primarily protects against HPV-16, HPV-18, HPV-6, and HPV-11 (Gardasil, approved by both the EMA [47] and FDA in 2006 [46]), and a nonavalent vaccine that protects against HPV-6, HPV-11, HPV-16, HPV-18, HPV-31, HPV-33, HPV-45, HPV-52, and HPV-58 (Gardasil-9, approved by the EMA in 2015 [48] and the FDA in 2014 [46]). After the approval for use in women, it took several years before the quadrivalent vaccine was also approved for men. The FDA expanded efficacy indications for men for the vaccines Gardasil and Gardasil-9 in respectively 2009 and 2015 [46]. The EMA adopted a positive opinion recommending Gardasil for the protection against ‘premalignant anal lesion’ and ‘anal cancer’ in 2014; no such adaptation was necessary for Gardasil-9, which was approved by the EMA for the protection against these lesions/cancers in Europe from the start in 2015 [47,48]. No such extensions are currently available yet for Cervarix.

The three HPV vaccines (bivalent, quadrivalent, and nonavalent) have proven to be highly protective against incident HPV, persistent HPV and associated cervical cancer endpoints
among a cohort of naïve women (i.e. women negative for HPV DNA and seronegative for the relevant HPV types, and with negative cytology at inclusion) and partially protective among young women with (previous) HPV exposure (non-naïve women). Furthermore, the bivalent and quadrivalent vaccines have shown some cross-protection against other oncogenic types not included in the specific vaccines [49,50]. HPV vaccine has also been shown to be effective in older (non-naïve) women [51–53] and was shown to be efficacious in MSM (non-naïve/HPV exposed) younger than 26 years and with less than 5 sexual partners [54,55].

The National Immunization Program in the Netherlands

In the Netherlands a government-defined set of vaccinations is offered free of charge. Vaccinations are offered at different time points during a child’s lifetime. Between the ages 1 through 4 years a child is vaccinated against childhood diseases at the Child Welfare Center of the Public Health Service, where they are offered the appropriate vaccinations during a periodic check-up consultation [56]. At the age of 9 years children are invited to a public venue designated by the Public Health Service to receive the necessary vaccinations against diphtheria, tetanus, and polio (DTP) and measles, mumps, and rubella (MMR) [56]. Examples of venues that are used are sports centers and child-and-parent centers. No personal consultation is offered during this vaccination moment. At 12 years old, girls are invited for their HPV vaccination at the same venues [56]. The child and parents/guardians receive their invitation one month before they are scheduled (together with all their age-peers) to receive their vaccination.

HPV vaccination in the National Immunization Program

In the Netherlands the HPV vaccination was introduced in 2009, which is now offered free of charge to all girls in the year they turn 13 years of age. After a call for tenders the bivalent vaccine was chosen for the Dutch program. The Health Council (an independent scientific advisory board for the Ministry of Health, Welfare, and Sports) advised to introduce the HPV vaccination [57] in the Netherlands. A group of cancer epidemiologists sounded a cautionary note stating that the seven criteria ([1] disease burden, [2] effectiveness, [3] safety, [4] acceptability of vaccine [burden versus health benefits], [5] acceptability of adding vaccine to the total program [burden versus health benefits in relation to the program as a whole], [6] efficacy, and [7] priority [58]) on which the Council had based its advice were only partially met and that introduction of the HPV vaccination was too hasty [59]. This fueled the debate on the utility of HPV vaccination in the Netherlands; this may have affected the public opinion towards the HPV vaccination negatively. In 2009 (the introduction year of the HPV vaccination in the Netherlands) the HPV vaccination uptake was only 52%, which was much lower than the childhood vaccinations for which the coverage has been well above 90% year after year [60]. In recent years the HPV vaccination uptake has slightly increased to 61% in 2014 [61]. This was, however, only 44% in Amsterdam and 46% in Rotterdam [62],
which is unfortunate as both cities have a higher number of diagnosed cervical cancer cases compared to the national average (11-12/100,000 women compared to 9/100,000 women nationally, \(p<0.01\)) [63]. The lower uptake of the HPV vaccination in Amsterdam and Rotterdam might be attributable to the higher proportion of inhabitants having a non-Dutch ethnic origin [64,65], as uptake among daughters of whom both parents have a non-Dutch ethnic origin appears to be substantially lower (24%-44%) than among those with both parents from Dutch origin (this was shown in a multi-level study regarding the uptake during the introduction of the HPV vaccination in 2009) [66]. Compared to other high-income countries the Netherlands’ performance is average, as the Europe-wide HPV vaccination uptake averages around 53% [67]. In line with guidelines of the European Medicine Agency the Netherlands decided in 2014 to reduce the HPV vaccination dose schedule from 3 to 2 doses, as studies showed that a 2-dose regime was non-inferior to a 3-dose regime, although a recent meta-analysis showed inconclusive results over longer periods [68].

The mode of delivery of the HPV vaccination varies around the globe, in the delivery strategy (school-based or health care facility), in the number of HPV doses (2 versus 3 doses), the target age, the genders included in the program (women only versus women and men) and the financing of the costs (government-provided, via health care insurance or [partial] personal contribution) [67]. Regarding HPV vaccination, Australia has as one of the most successful policies, as it has been able to reach high coverage in both the younger (~70%) (12-13 years old) and older (~50%) (18-26 years of age) targeted age cohorts among women [67], and has been able to show actual health benefits of vaccination [69,70]. Australia organized a catch-up for women aged 12-26 years from 2007 till 2009 and now offers routinely the vaccination to 12-13 year old girls and boys. Regions or countries were the HPV vaccination coverage are lowest are the USA (32% uptake; HPV vaccination is offered via primary health care provider and is covered by the insurance [if no insurance is available federally purchased vaccines should be available]), eastern Europe (e.g. Romania: 2-5% uptake; HPV vaccination is offered free of charge; country tried both school-based as well as health provider delivery strategies; program discontinued due to low uptake) and western Europe (e.g. France: 20% uptake; offered via health care providers, e.g. GPs; 65% of the HPV vaccine price is reimbursed) [67].

**HPV vaccination acceptability**

The above indicates that having an HPV vaccination program or policy in place will not necessarily prevent all (possibly not even the majority) of cervical cancer and other HPV related diseases -- uptake of the vaccination is crucial. Initial studies on HPV vaccination acceptability were conducted even before the HPV vaccine was licensed, resulting in studies with a highly hypothetical character [71–74]. Since HPV vaccination was introduced, studies on actual HPV vaccination intention have accumulated. In these studies several social-psychological theories have been used [75] with the ‘Theory of Planned Behavior’ [76] (most recent ver-
‘Reasoned Action Theory’ [77]) and ‘Health Belief Model’ [78] being the most prominent frameworks [75]. Overall, these studies highlighted the importance of social-psychological determinants (e.g. general attitude, beliefs, social norms, self-efficacy, perceived susceptibility and perceived barriers) when predicting HPV vaccination acceptance [75,79]. Factors shown to also influence HPV vaccination acceptance indirectly were for example cost of the vaccine and physician recommendation [75,79–81]. It should be noted that most studies are executed among women exploring the HPV vaccination acceptability at the time the HPV vaccination was introduced. These acceptability studies focused on the novelty of the vaccine devoting attention to e.g. long-term effectiveness of the HPV vaccine and uncertainties about side-effects; by now these factors may be less prominent yet they may emerge again when next generation HPV vaccines are introduced [75]. As research on determinants of uptake is accumulating, studies have focused on the effect of interventions on this uptake. Recent reviews on the effect of HPV vaccination interventions showed that HPV vaccination interventions may be most successful when different strategies are combined and indicated that one of the strategies reaching the strongest effect was the ‘reminder and recall system’ (e.g. phone calls and letters by mail, text messages by phone, and/or outreach activities) [82–84]. Furthermore, they reported that school-based interventions can reach high uptakes yet support from the community, availability of the vaccine within schools, and attendance of school are of key importance [83]. Finally the effect of educational interventions remains mixed [84,85], emphasizing the need for more research on the development of evidence-based intervention strategies (that can be applied in all types of settings) [82].

As mentioned earlier, HPV vaccination uptake in the Netherlands has been relatively low, presenting a clear need to understand and map the key determinants influencing the uptake of HPV vaccination. Recent studies focusing on the native Dutch population showed that socio-psychological determinants play a key role on HPV vaccine acceptance (e.g. attitude, concerns about vaccination effectiveness and safety, feelings of ambivalence towards HPV vaccination, anticipated regret, and normative beliefs) [86–89]. Based on the current mode of delivery of the HPV vaccination in the Netherlands (free of charge by the Public Health Service at a set time-point), GP initiated recommendations and costs of the vaccine do not affect the vaccination uptake of young girls in the Netherlands as has been found in international studies. Other factors that appeared to play a minor role in the process of decision making about the HPV vaccination were knowledge about the HPV vaccination, and knowing someone with an abnormal Pap test [86,87]. In view of the low uptake in ethnic minority populations [66] and the mounting evidence that introducing the HPV vaccination may be cost-effective among men [90], it is important to dissect the factors that influence the HPV vaccination intention and uptake in these groups. A thorough exploration of those factors will reveal whether these groups can be targeted in the same way as the native Dutch
population, or if e.g. ethnicity-specific implementation strategies are needed in order to maximize HPV-vaccination uptake.

CANCER SCREENING

The Pap (Papanicolaou) smear is currently the most widely used cancer test among women worldwide. It has contributed enormously to the decrease in cervical cancer deaths around the globe. Dr. Papanicoleau is seen as the founder of this cytological test, although Papanicoleau’s contemporary Dr. Babeş, developed a similar test – possibly at an earlier time [91]. The first work on the Pap test by Papanicoleau was published in 1928, yet it took until the 1940s --encouraged by J. Hinsey [92]-- to publish the groundbreaking study “The diagnostic value of vaginal smears in carcinoma of the uterus” by Papanicolaou and Traut [93]. Over the past decades the Pap smear has been one of the most successful techniques in the prevention of cervical cancer, saving millions of lives [94]. As a result cervical cancer became a preventable disease and advocacy of cervical screening programs started. In the Netherlands a pilot study for cervical cancer screening was initiated in 1976. More than a decade later, in 1989, a nationwide screening program was set up in which women aged 35 were screened every 3 years up to the age of 54 years [95]. The program was re-evaluated and in 1996 the testing interval was increased to 5 years (for individuals with a negative result) and screening was expanded to women aged 30 to 60 years [95,96]. Recent studies have shown that using hrHPV DNA detection as the primary screening test rather than cytology improves the effectiveness of cervical cancer screening [97–101] and it is therefore expected that in 2017 hrHPV DNA detection will be used as the primary test in the screening program [102]. Participation in the cervical cancer screening program in the Netherlands is 64% and is lowest in the largest cities, i.e. Amsterdam (51%), Rotterdam (49%), The Hague (49%), and Utrecht (56%) [103]. In a study among women invited between 1998 and 2001, cervical cancer screening participation was presented stratified by ethnic background, showing that participation varied by ethnicity: participation was 57% among Dutch, 51% among Surinamese, 48% among Turkish, and 36% among Moroccan women [104].

Screening for (precursors of) anal cancer, specifically in MSM, is currently not implemented and remains a matter of debate. The large variation in the way of “obtaining, processing or analyzing” anal smears and biopsies has been shown to result in varying degrees of sensitivity and specificity. It has therefore been proposed to combine cytology and histology screening as “a more sensitive measure of true disease” [33]. Furthermore, high-resolution anoscopy has not been shown to be straightforward and needs extensive training to be executed accurately. The use of hrHPV DNA detection as a primary test for anal cancer screening may also not be a good predictor of (precursor of) anal cancer as hrHPV prevalence in the anal
canal is high among MSM. Furthermore it has been found that after treatment recurrence of anal lesions can be high [105–108].

AIM OF THE THESIS

Definitions [109]

Ep·i·de·mi·ol·o·gy
/ˌepəˌdēmēˈäləjē/
noun
“The branch of medicine that deals with the incidence, distribution, and possible control of diseases and other factors relating to health.”

So·cial psy·chol·o·gy
/ˈsōSHəlsīˈkäləjē/
noun
“The branch of psychology that deals with social interactions, including their origins and effects on the individual[’s behavior].”

Minority
/məˈnôrədē/
noun
“A relatively small group of people, especially one commonly discriminated against in a community, society, or nation, differing from others in race, religion, language, or political persuasion”

This thesis provides a broad perspective on the epidemiology of HPV and the social- psychological aspects of HPV vaccination acceptability, among both women and men. The focus is on two different types of minority populations living in Amsterdam (the Netherlands) that are at higher risk of developing HPV induced disease: (1) people with a non-Dutch ethnic background, and (2) men who have sex with men.

Persons from various ethnic backgrounds

As mentioned above, HPV vaccination uptake in the Netherlands has generally been low, especially in certain ethnic groups [66], although these groups may benefit most from HPV vaccination as they exhibit a higher incidence of cervical cancer [36]. In order to unravel this health disparity, we take a two-fold approach: on the one hand mapping whether these
groups are also at highest risk of being HPV DNA or antibody positive, while on the other hand understanding what drives girls and their parent/guardians to (not) vaccinate against HPV. The insights gained may lead to more effective public health interventions that may help reduce ethnic health disparities in the near future.

**Men who have sex with men**
The Netherlands does not routinely offer HPV vaccination to men although men also can suffer from HPV induced diseases such as head and neck, penile, and anal cancer [33,110,111]. HIV positive MSM are disproportionally affected by these HPV induced diseases. Here, we investigate the epidemiology of HPV in male clients of the STI clinic and we assess their HPV vaccination acceptability. These data may be useful to assess the impact that HPV vaccination may have in these groups and can be used to design future HPV vaccination strategies.

Specifically, we aim to answer the following research questions:

**Part 1: How does HPV (sero-)prevalence vary by target group and are there specific risk factors for HPV (sero-)positivity?**
In Chapter 2 we describe how HPV infection (presence of HPV DNA) varies among six different ethnic groups living in Amsterdam, the Netherlands (HELIUS study). Next, we use HPV serological markers to explore whether HPV seropositivity differs across ethnicities in men and women residing in the same city (HELIUS study, Chapter 3). Within the same cohort we explore among women whether a genital HPV infection is an independent marker for HPV seropositivity and whether this varies by ethnicity (HELIUS study, Chapter 4). In Chapter 5 we analyze the association between site of HPV infection on HPV seropositivity among male clients of the STI clinic (DWAR study). In Chapters 6 (DWAR study) and Chapter 7 (HIM study) we investigate whether STIs may be independent risk factors for HPV (sero-)positivity among respectively male clients of the STI clinic and men from a multi-national study.

**Part 2: What are the most critical determinants in the process of decision making about the HPV vaccination?**
In Chapter 8 we present a longitudinal study (HP4V among parents/guardians study) on determinants of uptake among parents/guardians from different ethnic backgrounds. In Chapter 9 we explore the determinants of HPV vaccination intention among male clients of the STI clinic stratified by risk group (HP4V among men study).

Figure 2 presents a schematic representation of where Chapters 2-9 fit in the ‘HPV story’. The research presented within this thesis is executed in different study populations with different characteristics. Table 1 presents an overview of the different studies and characteristics of the study populations.
Figure 2. Putting the thesis into perspective. Chapters 2 through 9 discuss questions of HPV epidemiology and HPV vaccination acceptability in women and men.
Table 1. Characteristics of the studies and their study populations in which research questions of this thesis were examined.

<table>
<thead>
<tr>
<th>Study name</th>
<th>Geographic location</th>
<th>Study population</th>
<th>Source</th>
<th>Study Period</th>
<th>Chapter</th>
</tr>
</thead>
<tbody>
<tr>
<td>HELIUS study</td>
<td>Amsterdam, the Netherlands</td>
<td>Women from six different ethnic backgrounds aged 18-34 years</td>
<td>Random sample stratified by ethnicity from the general population</td>
<td>2011-2013</td>
<td>2 and 4</td>
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<tr>
<td>HELIUS study</td>
<td>Amsterdam, the Netherlands</td>
<td>Men and women from six different ethnic backgrounds aged 18-44 years</td>
<td>Random sample stratified by ethnicity from the general population</td>
<td>2011-2014</td>
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<tr>
<td>DWAR study</td>
<td>Amsterdam, the Netherlands</td>
<td>Men and women</td>
<td>Biannual HIV and STI and BBI survey among clients of the STI clinic of the Public Health Service (GGD) of Amsterdam</td>
<td>2008, 2009</td>
<td>5 and 6</td>
</tr>
<tr>
<td>HIM study</td>
<td>Sao Paulo, Brazil, Cuernavaca, Mexico, Tampa, United States</td>
<td>Men, aged 18-70 years</td>
<td>Men were recruited from three different population sources: general population, universities, and organized health-care systems</td>
<td>2005-2009</td>
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<td>HP4V among parents/guardians</td>
<td>Amsterdam, the Netherlands</td>
<td>Men and women with a daughter born in 2001</td>
<td>All parents/guardians with a daughter invited for the HPV vaccination in 2014</td>
<td>2014</td>
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<td>HP4V among men</td>
<td>Amsterdam, the Netherlands</td>
<td>Men</td>
<td>Clients of the STI clinic</td>
<td>2015</td>
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</tr>
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All studies are cross-sectional, except for Chapter 8 which is a longitudinal study. Abbreviations: HELIUS = HEalthy Life in an Urban Setting, DWAR = DWARsdoorsnede (bi-annual cross-sectional study); HIM = HPV in men; HP4V = human papillomavirus preparedness for vaccination; GGD = Geneeskundige en Gezondheidsdienst, STI = Sexually transmitted infection; HIV = human immunodeficiency virus; BBI = blood-borne infection.
REFERENCES


94. Wright JR. Cytopathology: Why Did It Take So Long To Thrive? Diagn Cytopathol. 2015;43.