HPV in minority populations

Epidemiology and vaccination acceptability

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CHAPTER 10

Discussion
In this dissertation we investigated the epidemiology of human papillomavirus (HPV) and HPV vaccination acceptability in various populations. We focused on ethnic minority populations and clients of the Sexually Transmitted Infection (STI) clinic -- specifically men who have sex with men (MSM) -- in Amsterdam, as it is known that these groups are disproportionally affected by HPV related cancers [1–3]. Thinking of these disparities, questions that immediately may spring to one’s mind are: How and why are these groups disproportionally affected? What can we do about this? Here, we address these broad questions by taking a two-fold approach. First we explore whether epidemiological data may provide possible explanations for why these groups are disproportionally affected. Next, we take a social psychological perspective to understand how primary prevention may decrease these disparities.

In each section we first put the problem in its historical or current societal context, subsequently we outline the findings of our research, relate them to recent literature, and finally we discuss how these findings may help to understand and reduce (and eventually eliminate) the observed disparities in HPV related cancers.

PERSONS FROM VARIOUS ETHNIC BACKGROUNDS

How does HPV (sero)positivity vary by ethnicity in men and women?

In Europe, non-western migrants are more prone to infection-related cancers, having a risk that is in between the risks of the general populations in the country of residence and their home country [4]. The Netherlands has an ethnically diverse population in which 22% (11% first generation [i.e. born outside the Netherlands and has at least one parents born outside the Netherlands] and 11% second generation [i.e. born in the Netherlands and has at least one parent who is born outside of the Netherlands]) of inhabitants are from non-Dutch ethnic origin. In total, 12% of the population has a non-western background (e.g. 2% with a Moroccan, 2% with a Turkish, and 2% with a Surinamese origin) [5]. The majority of this population is living in the larger cities of the Netherlands [6]. Amsterdam and Rotterdam, both multi-ethnic urban centers, have higher incidence rates of cervical cancer compared to the Dutch national average [7]. Stratified by ethnicity, women with a Surinamese, Moroccan, or Turkish background have higher incidence rates of cervical cancer [1,2]. The most common explanations for this higher incidence are a lower participation in cervical cancer screening programs [8–10], higher sexual risk behavior leading to increased exposure to HPV [11–13], or differences in HPV prevalence, distribution of HPV types, or persistence of HPV [14–16] making specific groups more prone to develop cervical cancer. However, none of these hypotheses have been unambiguously confirmed or refuted.
In Chapters 2, 3, and 4 we take a closer look at the roots of this disparity from various perspectives: the prevalence of genital high-risk HPV (hrHPV) infection (Chapter 2), seroprevalence of hrHPV (Chapter 3), and the relation between genital hrHPV infection with hrHPV seroprevalence (Chapter 4) in individuals from various ethnic backgrounds living in Amsterdam (i.e. Dutch, South-Asian Surinamese, African Surinamese, Ghanaian, Moroccan, and Turkish individuals). Our studies showed that South-Asian Surinamese women have a consistently lower (sero)prevalence of hrHPV than Dutch women. Among African Surinamese women on the other hand, we found that the prevalence of genital hrHPV infection was slightly lower, while hrHPV seroprevalence was higher when compared to Dutch women. The hrHPV (sero)prevalence of Ghanaian women was highly dependent on the age-group under investigation: Ghanaian women showed a lower seroprevalence of hrHPV when compared to Dutch women when the analysis was restricted to the age-group of 18-34 years, while the seroprevalence was higher compared to the Dutch when the analysis was done in the age-group 18-44. The explanation for this is that after the age of 30 the hrHPV seroprevalence among Ghanaian women strongly increased with age (yet the reasons for this finding remains unclear). In Chapters 2 and 3 we observed, perhaps unexpectedly, that women with a Moroccan or Turkish background had a lower (sero)prevalence of hrHPV than Dutch women. Despite the observed differences, after adjustment for differences in sexual behavior the non-Dutch women showed similar hrHPV (sero)prevalences as the Dutch group, implying that sexual risk behavior explains the observed differences to a large degree.

When interpreting the results of Chapter 2 one should keep in mind that this group of women concerns a ‘young’ cohort and that hrHPV infections are often transient. Furthermore, the persistent hrHPV infections that cause cervical cancer later in life are thought to be acquired at young ages. Regardless of whether infections acquired at a young age turn out to be transient or become persistent and possibly even lead to cancer, the cross-sectional nature of our study design prevents us from demonstrating temporality and therefore the results described in Chapters 2-4 at present do not lead to direct explanations for why non-western migrants experience higher incidences of cervical cancer. A longitudinal study of a multi-ethnic cohort in which HPV is sampled at different anatomical sites frequently, and the relation between HPV status and (pre-stages of) cervical cancer incidence could shed light on this. Furthermore, the results presented here are from a relatively young cohort while the disparities observed in cervical cancer incidence have been observed in a cohort composed of older women. It could very well be that these two cohorts are not similar enough to draw any conclusions regarding cancer disparities in women over the age of 45. Therefore, in spite of the lower prevalence of hrHPV in certain ethnic groups, continued monitoring of cervical cancer incidences stratified by ethnicity is highly advisable.
Keeping the above disclaimers in mind, we would like to provide some interpretations of the results and pose several hypotheses that merit further exploration. A previous study reported that women with an African-American background take almost twice as long as European American women to clear hrHPV infections in an analysis that adjusted for common risk factors like lifetime number of sexual partners and smoking [17]. Banister et al. hypothesized that the hrHPV variant infecting African-American women may be different (e.g. more oncogenic) and therefore could influence the clearance rate and the eventual development into cervical cancer [17–19]. It could also be that certain hosts, in this case African-American women, are genetically more susceptible to infection, persistence, or progression to cervical cancer [17,20–22]. This observation by Banister et al. [17] may help to interpret the overall higher hrHPV seroprevalence and lower prevalence of genital hrHPV infection observed among African Surinamese women when compared to Dutch women. Conjecturing from this, Surinamese women with African roots may suffer from hrHPV infections that persist longer and therefore may develop antibodies more often than Dutch women. In Chapter 4 we explored the relation between hrHPV infection with hrHPV seropositivity and found that being hrHPV DNA positive is an independent marker of hrHPV seropositivity after adjustment for confounders. We also tested whether this association was different across ethnicities but did not find any indications for this, although the observations described by Banister et al. [17] would suggest that such effect modification may exist. Yet the cohort under investigation in Chapter 4 was quite small which may have impeded our ability to find variation by ethnicity.

Among Moroccan and Turkish women, we observed a lower (sero)prevalence of hrHPV when compared to Dutch women, and these women most often reported only a single lifetime sexual partner. Therefore, if we temporarily disregard other existing risk factors, one might be inclined to say that men are responsible for introducing HPV in these groups. Based on this assumption, one could hypothesize that men would be the reason why Moroccan and Turkish women have a higher incidence of cervical cancer. However, assuming that sexual contact often happens with partners of the same ethnicity [23,24] and based on the results presented in Chapter 3, we do not have direct cues supporting this hypothesis. Specifically, even though we know that HPV serology may not be a perfect marker for past HPV infections among heterosexual men, we found that Moroccan and Turkish men had a slightly lower seroprevalence of hrHPV when compared to Dutch men. If Turkish and Moroccan men would indeed be hubs for the spread of hrHPV infection to Turkish and Moroccan women (eventually causing the observed disparities in cervical cancer incidence), we would expect these men to have higher hrHPV seroprevalences when compared to the Dutch men, which was not the case. Furthermore, it is known that the transmission of HPV from men to women is not as efficient as from women to men [25,26].
Alternatively, it is also possible that --although we know that naturally induced antibodies only provide modest protection for subsequent HPV infection among women [27]-- Turkish and Moroccan women may have a lower serological response, and therefore may be less protected against (new) persistent or subsequent infections. Another hypothesis is that, as this group of women has had low exposure to HPV in the past, they have had less chance to build up immunity, and this may result in low serological responses to HPV, leaving less protection against re-infection. The hypothesis of less protection against re-infection was put forward as a reason for why the risk to get HPV infected in life among men (having a lower serological response than women) may remain constant [28]. This line of reasoning arises from our observation in Chapter 3 that Moroccan and Turkish women had a similar hrHPV seroprevalence when compared to Moroccan and Turkish men, while it is known that hrHPV seroprevalence is typically higher in women than in men. This remained non-significant different in the Turkish group after adjustment for confounders, while in the Moroccan group women had a significant higher hrHPV seroprevalence than men after adjustment for confounders. This would suggest that (a) for a variety of possible reasons the immunological response in at least the Turkish women is not as strong as what we have seen for women from other ethnicities, or (b) HPV exposure has been extremely low in these groups of women (possibly leading to a low serological response) which could not be fully accounted for after adjustment for risk factors.

Many reports and studies focusing on individuals with a Surinamese background, regard the Surinamese as a single ethnic group, while this group in reality is quite diverse. The ethnically Surinamese population in the Netherlands, can be subdivided into Indo-Surinamese (in Dutch “Hindoestanen”) (45%), Creoles (39%), Javanese (6%), Chinese (3%), Maroons (3%), and a group of other, mixed or unknown (4%), where the ‘other’ category is composed of individuals with an indigenous native Surinamese background (Indians), Boeroes, and Lebanese [29]. In our study we showed that South-Asian Surinamese (mainly Indo-Surinamese) and African Surinamese (mainly Creoles) exhibit different hrHPV (sero)prevalence patterns, and therefore should not be taken as a homogeneous group. Monitoring of HPV prevalence or (pre-stages of) cervical cancer stratified by Surinamese subgroup could be of key importance, but the subgroups of Surinamese ethnicity are not consistently registered. Approaches that researchers have used to categorize the Surinamese group into subgroups include: using the family name of the person, using self-identified Surinamese background (as we did in Chapter 1-3), or using a combination of both [29,30]. Yet these approaches are cumbersome or need an additional step when registering a person. An improved and consistent method to categorize the ethnically heterogeneous Surinamese group would therefore be beneficial.
The above results do not lead to a complete understanding of the reasons for the observed disparities in HPV related cancers. From a public health point of view what matters most is that (1) certain ethnic minority groups are at higher risk to develop cervical cancer [1,2], (2) screening participation rates are lower among these ethnic groups [31,32], (3) 50% of the women diagnosed with cervical cancer are women who never participated in cervical cancer screening program [33], and (4) girls with a non-Dutch background are less often vaccinated against HPV [34]. Turning to the bigger picture and the question “What can we do about this disparity?”, several observations and recommendations can be made.

In the Netherlands a new approach to cervical cancer screening will be introduced (expected in 2017), in which hrHPV detection will be the primary screening test, and cytological screening will be done only if hrHPV DNA is detected. Also, a self-sampling device will be offered to those not attending screening [35]. Apart from the fact that hrHPV detection will be the primary screening test and therefore will be a goldmine from an epidemiological point of view, this may also help to confirm or refute the results presented in Chapter 2. Importantly, offering self-sampling devices may help to increase screening participation among (immigrant) women and eventually reduce the observed disparities. In a Dutch study in which self-sampling devices were offered to non-attendees, however, ~30% of invited non-attending women actually returned a self-sampled specimen [36]. This was lower (~20%) among women born in Suriname, Morocco, or Turkey [36]. The self-sampling group showed higher yields of cervical intraepithelial neoplasia 2 or worse (≥CIN2) and ≥CIN3 when compared to regular attendees. These results show that self-sampling will not be a magic bullet, but clearly self-sampling devices could help to increase uptake among non-attendees. Tailoring communication strategies to increase the uptake of self-sampling devices should be considered. However, research is necessary to assess determinants of (non-)uptake of self-sampling devices which may differ from determinants of (non-)participation of cervical cancer screening program (e.g. self-efficacy, anticipated pain during Papanicolaou test [Pap smear], and feelings of shame when a man takes the Pap smear) [37,38]. Based on a determinant study on (non-)participation of self-sampling devices, interventions could be developed accordingly.

Furthermore, continuous monitoring of cervical cancer screening participation and cervical cancer incidences (and mortalities) by ethnicity or other risk factors could be of key importance to identify groups at highest risk of cervical cancer. These groups may for example need tailored intervention to increase their participation in the screening program. Current data on disparities by ethnicity of cervical cancer incidence and mortality are based on individual population based studies of specific time-periods. To pursue such a goal, the standardized registration of ethnicity in the Dutch cancer registry (in the case of cervical cancer this is
stored within PALGA) via e.g. country of birth and country of birth of both parents, which is currently not the case, is of key importance, as has been suggested before [4,39,40].

Finally, while the cohort of vaccinated girls ages, it would be worthwhile to explore which groups of girls do (not) go for the HPV vaccination and which groups of women do (not) participate in the screening program of cervical cancer. By linking this to HPV status, (pre-stages of) cervical cancer incidence, and cervical cancer mortality, groups at highest risk may be identified. However, it will take at least 10 years before the youngest cohort of invited girls will turn 30; one could therefore consider linking cervical cancer screening behavior (including self-sampling devices, when introduced) of mothers, with the HPV vaccination behavior of their daughters. A previous study from Steens et al. [41] which investigated this association among girls invited for the HPV vaccination in the Netherlands in 2009 (when the catch-up program of the HPV vaccination was introduced) showed a significant association between mothers’ screening participation behavior and their daughters’ HPV vaccination uptake [41]. Steens et al. also showed that about half of the daughters with mothers that did not attend screening (23%) received the HPV vaccination. Moreover, they showed that girls with a non-western background are most likely to not participate in any of the two prevention methods. A recent study from the US showed that HPV vaccination is likely to reduce the overall burden of HPV related cancers among all ethnic groups, yet it is also likely to increase relative disparities across ethnicities [42]. We therefore suggest to repeat a similar exercise as done by Steens et al. when the new cervical cancer screening program with self-sampling devices is introduced, taking into account the (somewhat) higher HPV vaccination coverage and the new insights on HPV vaccination (e.g. herd immunity, long term effectiveness, possible availability of the 9-valent vaccine). This could provide us with further insights into how the epidemiology of HPV infection and cervical cancer in the Netherlands may evolve and whether other (or similar) target groups may arise.

**Do determinants in the process of decision making about HPV vaccination differ by ethnicity?**

Would epidemiological work on HPV, such as the research described above, still be necessary in a world where everyone is vaccinated against HPV? One may be inclined to answer this question with a ‘no’, assuming that in such a world HPV transmission would rapidly go to zero, and the observed disparities would therefore cease to exist. However, such a view is too optimistic. For instance, the currently licensed HPV vaccines do not protect against all HPV types. The vaccine that is currently used in the Netherlands (Cervarix) protects against the two major oncogenic HPV types (type 16 and 18) that are responsible for a large fraction (~70%), yet not all, cervical cancer cases worldwide [43]. However, in addition to protection against HPV types 16 and 18, cross protection against other types has been observed [44–46], increasing the expected vaccine efficacy. The impact of vaccination may be further
improved when the new nonavalent vaccine (Gardasil-9) would be used [47]. It is crucial to realize that even if a vaccine protecting against all oncogenic HPV types would be available, this would only have a major impact if the uptake of such a vaccine would be high. In the Netherlands it is estimated that with a 90% vaccination coverage of the bivalent HPV vaccine approximately 68% of all cervical cancer cases can be averted (increasing the HPV vaccination coverage to 100% would increase the percentage of averted cases with only ~1%) [48]. Considering the herd effect that vaccinating girls has on men, an estimated 66% reduction in the burden of HPV related cases among men is expected (at a 90% coverage among girls) [49]. Therefore developing powerful vaccines is only part of the story; the social dimension surrounding its implementation and uptake are also of vital importance.

In the Netherlands, the HPV vaccination is non-mandatory and is offered free of charge to all girls 12-13 years old. Unfortunately, the uptake has been relatively low and is stagnating at around 60% nationally (rising from 56% in birth cohort 1997 to 61% for the birth cohort of 2001) [50], and even lower in Amsterdam at just over 40% (41% in birth cohort 1997 and 44% in birth cohort 2001) [51]. A study by Rondy et al. [34] showed that the uptake of the HPV vaccination was drastically lower among girls if one or both of the parents of the girl were born outside the Netherlands. For example, 44% of the girls of whom both parents were born in Suriname received at least one dose of the HPV vaccination, if both parents were born in Turkey the uptake of at least one dose was 38%, while only a 24% uptake was reached among girls of whom both parents were born in Morocco [34]. The trend observed in the HPV vaccination coverage in the past few years shows only a very slight increase (1-2%) per year. Suppose a hypothetical scenario in which this trend, or maybe even a slightly more positive one of an increase in uptake of 3% every year, continues in the coming years. In such a scenario, without novel interventions to increase the coverage, it would take at least 10 years nationally, and even 17 years in Amsterdam, to reach a coverage as high as all other vaccinations given in the Netherlands (i.e. >90%, [50]) and probably even longer among specific ethnic groups. It should be noted that the National Institute of Public Health (RIVM) has adapted the content of the communication each year to actively increase the HPV vaccination uptake [52]. Yet the scenario outlined above may be somewhat worrisome, and interventions may have to be intensified or for some groups even developed from scratch.

As the HPV vaccination coverage has been especially low in ethnic groups that suffer from higher incidences of cervical cancer when compared to the national average [1,2,34], we explored in Chapter 8 whether parents with a non-Dutch background may benefit from interventions tailored to their ethnical background. Specifically, we investigated the first step (needs assessment) necessary to develop an intervention for e.g. communication strategies and invitation policies [53]. We assessed which determinants influence the decision making process concerning HPV vaccination among parents/guardians from different ethnic groups,
and whether the impact of these determinants are significantly different across these ethnic groups. The identification of such determinants provides the relevant targets for intervention development.

Chapter 8 concerns the determinants of HPV vaccine acceptability among parents living in Amsterdam from different ethnic groups. Ideally we would have compared all separate ethnic group with each other. However, as we did not had sufficient participants within each ethnicity, we combined ethnicities into four different groups by geography: Dutch (NL); Surinamese, Netherlands Antillean, and Aruban (SNA-group); Middle-Eastern and North-African (MENA-group); and Other. The MENA group was mainly composed of individuals with a Moroccan, Turkish, or Egyptian ethnicity. Parents received a questionnaire one month before their daughter was scheduled to receive her first HPV vaccine dose; in this way we aimed to disentangle intention from the actual behavior allowing us to explore the association over time between intention and uptake among these groups. We found intention to be the strongest predictor of the daughters’ HPV vaccination uptake. However, we also observed that the intention-behavior relation was weaker in the MENA- and SNA-groups when compared to the NL-group. This discrepancy was due to a larger fraction of inclined abstainers (individuals with a positive intention to vaccinate who eventually do not go for vaccination [54]) in the MENA- and SNA-groups when compared to the NL-group. The group of disinclined actors (individuals with a negative intention that eventually do go for vaccination) was very small and comparable across ethnic groups. A possible dissonance between an individual’s intention and uptake could be the presence of ‘logistical challenges’ that prevent one from getting the vaccination. However, if this were the case we would also expect a low uptake of the 9-year vaccinations (diphtheria-tetanus (DTP) and measles-mumps-rubella (MMR) vaccine) which are given at the same venues as the HPV vaccination. Interestingly, the uptake of the 9-year vaccinations among the girls in this study was extremely high, i.e. 97% in the MENA-group and 95% in the SNA-group in our study (Chapter 8). Similar high uptakes among these groups are also observed in the general population of Amsterdam [55,56]. We therefore hypothesize that parents changed their mind between the time that they completed the questionnaire and the actual day of vaccination. There may be a fraction in the MENA- and SNA-groups that in general thinks positively about vaccinating, yet, when confronted with negative arguments, is not able to counter those, and accordingly change intention and behavior. This is in line with previous observations made in the Netherlands, suggesting that parents initially go for vaccination out of ‘habit’ [57,58] or because they think it is ‘self-evident’ [59] and as a result easily change their mind when confronted with arguments against vaccination. As mentioned, the HPV vaccination uptake in these groups is very low and therefore the chance that these parents/guardians encounter other parents/guardians with negative attitudes and role model behavior is fairly high. New interventions may thus be necessary to change the overall negative attitude towards the vaccination in
this group to turn around the domino effect that may currently be working against HPV vaccination uptake. Further research is therefore needed to unravel what is making non-Dutch parents change their mind more often than the Dutch parents.

The explained variance in HPV vaccination intention (rather than actual HPV vaccination uptake) in all ethnic groups was best and to a large extend explained by so-called proximal social-psychological determinants: i.e. attitude, beliefs, risk perception, subjective norms, and descriptive norms. When testing whether the impact of the determinants differed across ethnic groups, we found that the strength of associations with both intention and uptake were largely similar across ethnic groups. We therefore conclude that communication strategies for the different ethnic groups should target similar determinants. Although there is no critical need for developing separate communication strategies for these different ethnic groups, the mode of delivery of the information might still need to be tailored. We suggest the latter, as we observed that a large fraction of the MENA-group needed help with completing the questionnaire of this study. This is in line with other studies that have found language to be a barrier for successful communication [60–62].

Current policy of the Amsterdam Public Health Service (GGD) states that information should only be offered in Dutch or English. In contrast, the aim of the RIVM is to offer information in various languages on the RIVM website [61,63], yet no such information is currently available in languages other than Dutch or (an abbreviated version in) English. In our view the present situation may be entitled as a ‘Catch-22’ [64]; the Public Health Service is not allowed to offer the information in another language than Dutch or English, while the RIVM aims to offer such information in other languages but does not have this information readily available. Moreover, if this information would be available on the RIVM website the question remains whether the parents most in need of this information will be able to actually access this website and find the information they need. We therefore suggest evaluating whether offering this group written or oral information in their native language would result in a higher uptake of the HPV vaccination, as has been suggested previously [60–62]. As language barriers are a topic that surfaced several times over the past years, one could consider to grasp the nettle and immediately start offering the HPV vaccination information leaflet in several languages (e.g. Turkish, Arabic, and English) in the larger cities of the Netherlands and, if successful, implement this nationally. However, it is known that Arabic is mainly spoken by the higher educated part of the Moroccan community and therefore oral communication in Berber (a language that is known to have different dialects and mainly used verbally) should not be overlooked.

The RIVM is currently setting up a monitoring system to evaluate (changes in) determinants of parents’ decisions concerning vaccination uptake [63]. One of the elements that has
been proposed within this monitoring system, is to send out a monthly questionnaire to a sample (~20%) of the parents before their daughter/son is invited for one of the vaccinations given at ages 1-4 years [63]. The rationale behind sending a questionnaire to the 1-4 year old group is to monitor possible changes in determinants of uptake. However, it may be a missed opportunity to not include the other vaccinations within this monitoring system, and therefore also monitor (changing) determinants influencing the uptake for the 9-year old group and the uptake among 12-year old girls. The questionnaire regarding HPV vaccination that was successfully tested in a predominantly Dutch group of parents [58] and that has been adapted for an ethnically diverse group (Chapter 8), and for male clients of the STI clinic (Chapter 9), might provide a solid basis to periodically monitor determinants of HPV vaccination uptake.

The questionnaire used in Chapter 8 covered some aspects that were not reported in Chapter 8. Some of those additional results, however, may be informative for future interventions and thus merit further discussion. The location where parents/guardians indicated they would like to have their daughter vaccinated (parents could choose from various options), is an example of this. The most popular option was the general practitioner (67% in the NL-group, 61% in the SNA-group, 51% in the MENA-group), and the second most popular option was the child vaccination clinic, where vaccinations between 1 and 4 years of age are administered (41% for NL-group, 59% for the SNA-group, 44% in the MENA-group). Only 22% of the parents from the MENA-group and around 35% in the other groups, indicated they wanted their daughter to get vaccinated at the location where it is offered currently. In our opinion, this is a signal from parents that they desire a contact moment with a professional to be able to talk about the HPV vaccination. One could consider (temporarily) combining the HPV vaccination with another contact moment. At the STI clinic of the Public Health Service of Amsterdam for instance, HPV vaccination will be offered to girls aged less than 19 years visiting the Sense consultations (these consultations are offered to young people with questions regarding sexuality or anticonception). The aim of this program is to reach girls at highest risk. Another possibility could be to combine the HPV vaccination with for example the 10-year examination of the Youth Health Service of the Public Health Service of Amsterdam. The 10-year examination is a fixed moment during which the Youth Health Care from the Public Health Service currently has contact with the girl and her parents. Additionally, one could imagine a scenario in which parents need to sign a form if they do not want their daughters to be vaccinated against HPV (opt-out) during for example the 2nd grade-examination (a contact moment of the Public Health Service with girls). Ethical issues should be taken into account using this strategy. Two countries that use the opt-out strategy are Australia and the UK which probably due to a combination of e.g. opt-out strategy and the way of delivery (i.e. girls are vaccinated at school) is achieving vaccination rates up to 80% (age target group 12-13 years) [65]. By combining the HPV vaccination with an already
existing fixed contact moment (in principle unconnected to HPV vaccination), a professional can engage in a conversation with the daughter or parents/guardians to talk about concerns relating to the HPV vaccination. For such an intervention to be successful, training of these professionals is necessary to learn to communicate with (critical or hesitating) parents about the HPV vaccination [63]. Also possible language barriers and the (limited) time available to provide such information during a consultation should be taken into account. Vaccinations have been provided in the Netherlands in the same way for several decades. However, in the case of the HPV vaccination it merits further exploration whether we should continue on the current track or whether there may be better ways of delivering the HPV vaccination. Finally, to improve the general attitude within a community, an intervention targeting different levels (media, politics, health-care professional, schools, parents and daughters) is of key importance. Recent reviews measuring the effect of different types of intervention on HPV vaccination uptake have shown that interventions using different strategies (patient reminder and recall system, patient education, community-based intervention, provider reminders, healthcare system-based, and finally vaccination programs in school) on different levels (informational, behavioral, and environment) have reached the highest effect [66–68]. Further research is needed to explore how such interventions could be translated to the Dutch setting. As it has rarely been observed that a single theoretical model fully predicted and when implemented changed an individuals’ behavior, it is important that approaches like Intervention Mapping [53] are used to build a more integrated theoretical base for designing an HPV vaccination campaign that helps to decrease the currently observed disparities.

**Men who have sex with men**

In this section we investigate the epidemiology of HPV in men and assess their HPV vaccination acceptability. We focus on MSM, as MSM, especially HIV-positive MSM, are disproportionately affected by HPV induced diseases.

**Does the site of exposure predict HPV seropositivity?**

At the time Chapter 5 was published, the association of the anatomical site of exposure as a predictor for HPV seropositivity was not well understood, although it was known that women and MSM had higher HPV seroprevalences than heterosexual men. In Chapter 5 we addressed this question and demonstrated that the site of exposure indeed is an independent risk factor for HPV seropositivity. We showed that the odds to be hrHPV seropositive are equally high for MSM reporting receptive anal sex and women reporting sex with men. We also showed that MSM who only reported insertive anal sex had equal odds as heterosexual men. The odds to be hrHPV seropositive were significantly higher in women and MSM reporting receptive anal sex when compared to MSM reporting insertive anal sex only and heterosexual men. All these associations were corrected for important confounders. These results suggest that the humoral response induced by an HPV infection at keratinized
epithelium (e.g. penile shaft) is lower than the response induced by an infection at mucosal epithelium (e.g. cervix or anal canal). This conjecture also suggests that differences in sero-prevalence between men and women are not a gender difference per se, but arise from differences in the type of epithelium that is exposed. Alternatively, it is also possible that HPV exposure of the keratinized epithelium less often leads to a successful infection compared to exposure of mucosal epithelium and therefore no humoral response is triggered.

Presently, the anatomical site of exposure is an established predictor of HPV seropositivity [69,70] and the discussion has moved on to whether naturally induced antibodies protect against new infections with HPV. The few studies that have explored this association thus far, have shown no protection against subsequent HPV infection among men [71–73] and modest protection among women [27]. Yet the implications of these findings may be more of academic rather than practical importance, as it is known that vaccine induced antibody concentrations are 10-40 times higher than naturally induced antibody concentrations, and are shown to be almost 100% effective against new HPV infections of types included in the vaccine [74–76].

**Are STI risk factors for HPV (sero)positivity?**

Since the start of the AIDS epidemic in the early 1980’s, more than a decade passed before the link between STI and the human immunodeficiency virus (HIV) was fully acknowledged [77,78]. This link was first shown in studies with measurements at a single point in time (e.g. case-control and cross-sectional studies), but those results were questioned because of the shared route of transmission and –inherent to cross-sectional and case-control studies— the impossibility to establish a temporal relation [78]. As longitudinal studies accumulated, the relation between STI (both ulcerative infections and non-ulcerative infections) and HIV became firmly established [78–83]. Alongside fundamental biological studies investigating the mechanisms of HIV infection, it was shown that STI-infected individuals were more susceptible to infection with HIV, because STIs break down the mucosal barrier and increase the number of susceptible cells (e.g. T-helper cells and macrophages) in the mucosa caused by inflammation [84]. Also the converse turned out to be true: HIV infected individuals are more infectious when infected with an STI if no other intervention/suppression methods are taken [78–81,83,85,86].

It may be somewhat ironic to realize that it was first thought that cervical cancer was caused by herpes simplex virus-2 (HSV-2) [87], as the associations between HSV-2 (among other STI) with both HPV and cervical cancer are probably easily confounded, because HPV and HSV-2 share the same route of transmission. In analogy with the story of HIV, and the fact that HPV is the necessary, but not sufficient cause of cervical cancer, researchers have been encouraged to explore the influence of other non-HPV STI on the natural history of HPV
infections and the etiology of cancer induced by HPV [88]. Most studies show strong associations between non-HPV STI with HPV, yet no clear conclusions have been drawn as contradictory results have also been published [89–98]. The majority of studies on the association between non-HPV STI with HPV focus on women. Here we explored the association between HPV and STI among men of the general population and MSM visiting the STI clinic. Both populations are of interest as heterosexual men are responsible for the vast majority of transmission to women, while MSM have the highest burden of HPV related cancer. In a cross-sectional study among MSM visiting the STI clinic of the Public Health Service in Amsterdam, HIV was an important risk factor for HPV seropositivity (Chapter 6). In a cross-sectional study among men of the general population we observed a significant association between both Chlamydia trachomatis (CT) and HSV-2 with HPV infection (Chapter 7). Both studies adjusted for confounders, including sexual risk behavior. Now that more data on this topic are accumulating, a possibly useful scenario may be that MSM who have a history of an STI follow another anal-screening protocol than individuals who never had an STI (e.g. more frequent follow-up and/or possibly a less conservative approach). Even if the transmission route between non-HPV STI with HPV and HPV related cancers may confound the association, such a screening strategy could prove fruitful. Women with cervical cancer for instance, more often have antibodies against CT compared to women not having cervical cancer, indicating that individuals with a history of an STI --even if it would not be biologically induced but confounded by higher sexual risk behavior—are at higher risk to have an HPV related disease [88,92,93,99,100]. Perhaps among MSM, who usually have a higher prevalence of HPV limiting the utility of HPV DNA as an indicator, an STI history could be a useful indicator for a different screening protocol (although the practicality of this remains to be assessed). However, primary prevention of STIs in general should remain the main public health focus.

**What is the HPV vaccination intention of young men visiting the STI clinic?**

In the Netherlands men are not routinely vaccinated against HPV. As mentioned above, HPV vaccination is currently (2016) only offered free of charge to girls (12-13 years of age). Based on the current coverage among girls (~60%) in the Netherlands [50], men benefit indirectly from the HPV vaccination through herd immunity [49,101,102]. Mathematical models predict that an HPV vaccination coverage of 60% among women in the Netherlands, reduces penile and male oropharyngeal cancer cases by ~50%, yet may only achieve a modest reduction of 18% in male anal cancer cases, as herd immunity from vaccinating girls is assumed not to affect cancer cases attributable to men-to-men contact [49]. The indirect protection among heterosexual men is highly dependent on the HPV vaccination coverage among girls. It is unclear if and when vaccination of young boys in the Netherlands will be introduced, and one may therefore consider starting by vaccinating men at highest risk, e.g. MSM and heterosexual men visiting the STI clinic. Heterosexual young men visiting the STI clinic may be considered at higher risk for acquiring HPV infections and may be viewed as an important
group to target for HPV vaccination. Probably the most important group are MSM visiting the STI clinic, as those men generally do not profit from herd immunity from vaccinated girls and are disproportionally affected by HPV related cancers. Whether vaccinating male clients of the STI clinic is effective in decreasing the HPV prevalence depends on a number of factors (e.g. transmissibility of HPV and HIV status), yet uptake of the HPV vaccination may be one of the most important factors [49].

In Chapter 9 we therefore investigated the intention to get vaccinated against HPV among male clients of the STI clinic. We found that both heterosexual men and MSM visiting the STI clinic have a high intention to get vaccinated against HPV; this intention was significantly higher among MSM than among heterosexual men. In multivariable analyses we found that attitude and self-efficacy (measured as the perceived ability of going to the STI clinic three times to get the complete series of HPV vaccinations) were the most important determinants of intention. When testing whether determinants had a significantly different effect on intention in MSM compared to heterosexual men, we found a similar effect of most determinants on intention among both groups, except for subjective norm, self-efficacy, and knowledge which all three were stronger among heterosexual men than in the MSM group. Subjective norm is a measure used in social psychological research in which two aspects of someone’s social environment are taken into account: (1) what does an individual believe that another important person expects she/he to do, and (2) what is an individual’s motivation to comply with the perceived expectation of this important person. Among heterosexual men, we found that the stronger they perceived that their friends and sex partner(s) expected them to get vaccinated, the higher their intention. However, the motivation to comply with these expectations was low with respect to their friends, but high with respect to their general practitioner (GP) or sex partner(s) (data not shown in Chapter 8). Self-efficacy, measured as the perceived ability to go to the STI clinic three times to get the complete series of HPV vaccinations, had a stronger effect on intention among heterosexual men when compared to MSM. Possibly MSM visiting the STI clinic perceive visiting the STI clinic as less of a challenge than heterosexual men, which may be influenced by feelings of embarrassment associated with visiting the STI clinic and by the (un)familiarity with visiting the STI clinic (i.e. a larger proportion of MSM visit the STI clinic more frequently than of heterosexual men [103]; this group of MSM may therefore have more experience with this behavior and perceive this as less of a barrier). Please note that self-efficacy was a significant predictor in both groups, only with a significantly stronger impact on intention in the heterosexual men group than in the MSM group. We also explored what the effect would be of asking men whether they would still be inclined to get the HPV vaccination in case they had to pay for it. The intention of men to get vaccinated appeared to decrease dramatically with increasing costs. If the HPV vaccination was offered free of charge the vast majority of men indicated that they certainly wanted to get vaccinated. Yet if the three vaccinations were offered for €50 (one-seventh of
the price when buying it at the pharmacy) the intention decreased almost with a full point on a scale ranging from -3 to 3. When the total price of three vaccines together was €350 the intention became negative.

It is clear that if the HPV vaccination is not offered free of charge the intention to vaccinate decreases dramatically. In case the HPV vaccination would be offered free of charge, an HPV vaccination program focused on clients of the STI clinic could be very successful at reaching a high coverage by targeting attitudinal factors (beliefs, negative outcome expectancy, and anticipated regret when rejecting the HPV vaccination), social influences (friends, GP, nurse STI clinic, and sex partner[s]) as well as self-efficacy (perceived control regarding visiting the STI clinic three times). Most studies on vaccination acceptability in the Netherlands have shown that the process of decision making about vaccinations is to a large part attitudinally driven [57,63], yet in this group of men we found social influences and self-efficacy to also play an important role. Attitude was still one of the most important predictors, although self-efficacy showed the second highest association with intention in both groups suggesting that HPV vaccination programs among these groups should not only target attitudes but also perceived behavioral control determinants associated with visiting the STI clinic three times. A simple way of overcoming feelings of embarrassment associated with visiting the STI clinic could be by offering the HPV vaccination through the GP, which may also increase adherence.

The results of Chapter 9 should be perceived as a first step (needs assessment) to systematically develop a theory- and evidence-based intervention. Leads for developing the next steps in planning such an intervention are provided by e.g. the Intervention Mapping framework [53]. Further research may be necessary to reveal (1) whether the intention of these men will translate into actual uptake of the vaccination, (2) whether awareness about the low uptake of the HPV vaccination among young girls influences HPV vaccination intention and uptake of these men, and (3) what the impact of targeted HPV vaccination of male clients of the STI clinic, in particular MSM, would be on the public opinion concerning HPV vaccination. In other words --in analogy to the Hepatitis B vaccination—it may be possible that the public will perceive the HPV vaccination as a vaccination that is only necessary for individuals with high sexual risk behavior and men having sex with men. The Hepatitis B vaccination was first introduced in 2003 by offering it to higher risk groups e.g. MSM and children from specific risk groups. It was feared that the uptake of the Hepatitis B vaccination, when offered within the national vaccination program, would be low as parents might perceive their kids not to be at risk. However, the hepatitis B vaccination was, almost silently, introduced in the regular vaccination program in 2011 with high uptakes [50]. Yet the stigma that may rise from a vaccination that is offered to groups with high sexual risk behavior should not be overlooked, as vaccination of young boys may also become a reality, and a negative percep-
tion regarding the HPV vaccination by the public may not be easy to reverse. It is therefore of key importance to evaluate how to position and formulate a targeted HPV vaccination among male clients of the STI clinic within the current public debate of HPV vaccination. One may be inclined to discount this as a non-issue, as the hepatitis B vaccination was also initially offered to high-risk groups. However, there is an important difference between the implementation of these two vaccinations as the hepatitis B vaccination was offered within a cocktail with other childhood vaccinations [104,105], while HPV vaccination is offered separately, on a different moment, and at a different age.

RECOMMENDATIONS

In the above discussion we outlined challenges, lessons learned, and suggestions for future research and monitoring. Here we highlight the most prominent recommendations concerning monitoring & surveillance, the embedding of the HPV vaccination in the National Immunisation Program, and further research.

Monitoring & surveillance
- Current data on cervical cancer screening participation and incidence (and mortality) of cervical cancer by ethnicity are based on individual studies. We recommend standardized registration of ethnicity in the Dutch cancer registry, as this is currently not the case. This would allow participation in screening, HPV prevalence, incidence (and mortality) of cervical cancer, and (eventually) HPV vaccination status to be monitored by ethnicity (based on country of birth of the woman and both of her parents) nationally.

- Registration of ethnicity may also allow to assess whether cervical cancer disparities by ethnicity will continue to be observed and what the contribution of non-participation in screening and HPV vaccination will be to the burden of HPV related diseases in the Netherlands. Until the moment that the first HPV vaccination cohort of girls is at least 30 years old, and the relation between cervical cancer, screening participation and HPV vaccination within the same individuals can be monitored, we suggest to explore the association between HPV vaccination status of girls and cervical cancer screening participation of their mother. Exploring this association would be even more interesting after self-sampling devices are introduced within the cervical cancer screening program.

- We recommend that the RIVM includes monitoring (changes in) determinants of HPV vaccination uptake among parents/guardians and their daughters in its recently introduced vaccination monitoring system.
Adapting the HPV vaccination program

- We strongly recommend that HPV vaccination information is offered in the native languages of ethnic groups in which the HPV vaccination uptake is lowest and that information in the respective languages is added to the current information materials provided when inviting girls for HPV vaccination. Furthermore we recommend to not only provide this information in written form but also verbally (e.g. face-to-face, group meetings, etc.).

- In our opinion a clear national strategy about national and/or targeted male HPV vaccination should be formulated. While awaiting such a national strategy we believe that vaccination of male target groups, such as clients of STI clinics, should be evaluated without further delay. If and when vaccination to male clients of STI clinics is implemented, caution is needed to avoid that HPV vaccines are perceived by the public as vaccines for people with high sexual risk behavior.

- A previous study in the Netherlands estimated that girls with a non-western ethnicity are probably at highest risk for non-participation in cervical cancer screening and/or HPV vaccination programs. In about ten years the first cohort of girls that was invited for the HPV vaccination will be invited for their first cervical cancer screening. As long as the uptake of HPV vaccination has not reached its optimal level among ethnic minority populations, we suggest to maintain the ‘double Dutch’ principle in which intensified programs are developed to increase the uptake of HPV vaccination and cervical cancer screening in these groups.

Future research

- In Chapter 2 and 3 we observed that HPV (sero)prevalence is lower among South-Asian Surinamese when compared to African Surinamese. No current data on (prestages of) cervical cancer incidence and cervical cancer stratified by Surinamese subgroups are available. We recommend to investigate the epidemiology of cervical cancer stratified for the individual Surinamese subgroups. To facilitate such a line of research, one could develop an automatic computer algorithm to categorize Surinamese into the ethnic subgroups. If disparities would indeed be observed one could consider using such a system (or registration of self-reported ethnicity) for screening, monitoring, and surveillance programs.

- Studies that explore HPV incidence, persistence, clearance, and related sequelea among women by ethnicity are very scarce. The Healthy Life In an Urban Setting (HELIUS) study provides ample opportunity to explore similar questions within the Dutch setting and we suggest that such a follow-up study is embedded in the HELIUS study.

- The research described in Chapter 8, together with previous studies, presents a clear overview of the determinants of HPV vaccination acceptability among girls in the Netherlands.
Taking advantage of this knowledge, the focus should now shift to clearly identify on which channels should be focused to provide the HPV information and offer the HPV vaccination, what the credible sources of information are, and which theory-based intervention methods and practical applications should be used to target the proven important determinants of HPV vaccination uptake. We therefore recommend the development and evaluation of theory- and research-based interventions to increasing HPV vaccination uptake. Such work should keep in mind the costs, the possibility of the introduction of another type of vaccine (e.g. 9-valent) (which may re-open the public debate on HPV vaccination), as well as the possibility that we may not be far from offering HPV vaccines to (young) men.

- Further research is important to explore the reasons why a subgroup of parents with a positive intention eventually does not go for the HPV vaccination.

- If and when HPV vaccination is offered to male clients of STI clinics, a study on determinants of actual HPV vaccination uptake is necessary. Such a study should elucidate determinants of actual uptake rather than determinants of a hypothetical scenario of a vaccination (as was done in Chapter 9).

- If and when HPV vaccination is offered to male clients of the STI clinic, research is needed to develop theory- and research-based interventions that will result in high HPV vaccination uptakes.
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