Interventions for STI control: vaccination and testing
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General discussion
The overall theme of this thesis is the effectiveness of STI interventions. We focussed on questions such as whether current implemented interventions are effective, need improvement, or whether new interventions need to be implemented to control the STI epidemic in the Netherlands. Two specific interventions for STI control were examined in this thesis in more detail, namely vaccination against HPV (Chapter 2) and testing for STI among MSM (Chapter 3). In Chapter 4 we provide insight into the HCV epidemiology of the general population to inform screening programs.

HUMAN PAPILLOMAVIRUS IN A SEXUALLY ACTIVE POPULATION

Monitoring the effects of HPV vaccination
Based on the high efficacy of the HPV vaccine against cervical cancer observed in RCTs and cost-effectiveness studies, the Netherlands implemented HPV vaccination in the national immunisation program in 2009. The PASSYON study is one of the Dutch studies set up to monitor the effect of HPV vaccination in the population. The PASSYON study focusses on young male and female STI clinic attendees aged 16- to 24-years old. In the first wave of the PASSYON study, participants had a high prevalence of infections with a high-risk HPV type, as was shown in Chapter 2.1: 39.5% positivity in heterosexual men and 58.2% positivity in women. The probability of finding statistically significant differences in type-specific HPV prevalence depends on sample size and effect size. Based on the large HPV prevalence found in this sexually active population, it is expected that the effect size of vaccination within this subpopulation will be larger than seen in Dutch monitoring studies of populations with lower HPV prevalence rates. Therefore, effects of vaccination are expected to be first observed in this highly HPV-prevalent study population.

From 2008 till 2012, England implemented the same vaccine as the Netherlands, using a school-based vaccination program [1]. A vaccine coverage of 80% was reported, which was higher than the 60% vaccine coverage reported in the Netherlands. Recently England published their first results on the impact of vaccination, showing lower HPV16/-18 prevalence rates post-immunisation in comparison to pre-immunisation [1]. In our monitoring study, we have not yet seen effects. However, the first wave of the cross-sectional PASSYON study (2009) was a baseline measurement (Chapter 2.1) performed prior to vaccination. In the second wave (2011), as vaccination coverage among female participants was still low (6%), no effect of vaccination was to be expected. In the third wave (2013), the 13- to 16-year-old girls vaccinated during the catch-up campaign in 2009 reached the age of 17 to 20 years, bringing the proportion of girls being vaccinated to 19%. This third round therefore has the potential to show the first effects of vaccination within this specific age group. Future rounds will be of even more interest, since the proportion of girls aged 16 to 24 years being vaccinated will further increase.

In the Netherlands, the PASSYON study is unique in focussing on young MSM as well as young heterosexual men (and women), a combination lacking in other ongoing Dutch studies [2, 3] and rare in international HPV studies. HPV DNA is regularly found in cancers of the penis.
(40 – 50%) and in anal cancers (88 – 94%) [4]. In most noncervical cancers, HPV16 is the most common type detected [4]. Chapter 2.2 showed that 9% of heterosexual men and 4% of MSM had a penile HPV16 infection. Since MSM often report anal intercourse, we tested anal as well as penile swabs for MSM, finding 11% positivity for HPV16 at the anal region. These results indicate that both male subpopulations are at risk for premalignancies of the penis and that MSM are especially at risk for anal cancer. It was estimated that with a vaccine coverage of 70% in girls, the HPV16/-18 prevalence could be reduced by 64% in the total population [5], but its reduction in the MSM population would be negligible [6]. With the current vaccine coverage of 60% among young girls, it is of interest to study the extent to which effects of vaccination will be noticeable in heterosexual as well as bi-/homosexual men. To optimize the percentage reduction of HPV prevalence in the overall population, one could not only increase the uptake among girls but also consider extending HPV vaccination to boys of similar age. However, the incremental gains in herd immunity from vaccinating boys and girls versus vaccinating girls only were predicted to be modest [6, 7] and not cost-effective [8]. Instead of extending vaccination to boys, one could consider targeted HPV vaccination for MSM, since MSM are a population in which the prevalence of anal cancer is rather high, especially among HIV-infected MSM [9]. Despite the lower vaccine effectiveness when vaccinating a population that is already exposed to HPV infections, vaccination of MSM remains cost-effective in MSM up to 26 years of age when assuming a 50% vaccine efficacy reduction due to prior HPV exposure [10].

Observational studies are constantly affected by external factors. An important factor in the Netherlands has been the change from a three-dose vaccination schedule to a two-dose schedule in January 2014. The reduction in doses was based on the marketing authorisation granted by the European Medicines Agency (EMA, www.ema.europa.eu) for a two-dose vaccination schedule with Cervarix®, since immunity against HPV among girls up to 15 years of age appeared to be equally high after two vaccine doses compared to three doses [11]. This change in vaccination schedule makes it important to know the number of vaccine doses per individual and the vaccination coverage rates at population level. Such information is required to interpret future data, to judge vaccine effectiveness, and to assess whether a two-dose schedule is indeed comparable to a three-dose schedule in the long run.

In the PASSYON study, as well as many other studies, the highly sensitive DEIA test is used in combination with a LiPA to detect HPV DNA in vaginal, penile and anal swabs. This combination is an expensive and time-consuming method. A much cheaper and easier method would be to determine HPV antibodies in serum. However, the association between DNA and antibodies is poor, as HPV16/18 infections will result in detectable antibodies in up to 60% of sera [12, 13]. In addition, infections of the dry keratinized tissue of the penis tend to seroconvert less often in comparison to infections of the soft mucosal tissue of the vagina and anus, as described in Chapter 2.2 and other studies [14, 15]. Based on this knowledge, one must interpret results of HPV serology with care. The extent to which HPV antibody detection tests at population level can support monitoring purposes should be further explored. Measuring HPV DNA as well as HPV antibodies over a certain time span and comparing trends of HPV prevalence between these methods could give more insight into these dynamics.
Factors influencing HPV infection
Although vaccination has probably the largest impact on the occurrence of HPV infection, other factors could play a role in the infection process. For example, in Chapter 2.1 it is shown that practicing high-risk sexual behaviour increases the odds of infection with a high-risk HPV type. In addition, concurrent STIs could make a person more susceptible for HPV. In Chapter 2.3 it was observed that *Chlamydia trachomatis* (hereinafter, chlamydia) was associated with the presence of incident HPV infection after adjustment for sexual behaviour. There were also indications that chlamydia could delay the clearance process of an existing HPV infection. The latest epidemiological studies on the impact of a chlamydia infection on HPV acquisition and persistence yielded equivocal results due to the difficulty of separating biological from behavioural effects. For example, HPV and chlamydia share their route of transmission: both infections are sexually transmitted. By including sexual behavioural factors as covariates and stratifying the analyses for HPV genotype, we made it possible to estimate an independent effect of chlamydia on type-specific HPV infection, although residual confounding cannot be excluded. The type-specific character of the analyses made it a unique study [16-18]. The results of Chapter 2.3 indicate that not only practicing safer sex could help in preventing HPV infections, but also tracing and treating chlamydia in a young sexually active population could be beneficial.

Impact of anogenital warts
Anogenital warts are common, and their presence has an impact on emotional well-being and sexual activity, as shown in Chapter 2.4. In this study it was found that women experience more discomfort than men and that the impact of warts on well-being was influenced not only by clinical symptoms but by sexual characteristics as well as. We concluded that the prevention of anogenital warts would, especially in young women, prevent loss in health related quality of life.

Anogenital warts can be prevented by vaccination. However, the bivalent vaccine implemented in the Dutch immunisation program does not target wart-specific HPV types. Although recent studies observed that the bivalent vaccine has partial efficacy against these types [19, 20], its effectiveness in preventing anogenital warts will probably remain suboptimal. To prevent anogenital warts more effectively, one could consider introducing the quadrivalent HPV-vaccine in the Netherlands, protecting against HPV-6, -11, -16, and -18. This vaccine has already significantly decreased the incidence of anogenital warts in Australia [21].

**STI TESTING IN MEN WHO HAVE SEX WITH MEN**

HIV-negative MSM
In Chapter 3.1 we estimated that two thirds of HIV-negative MSM at the Amsterdam STI clinic returns within 4 years for a subsequent STI test, whereas approximately a third returns within a year. In the first two years following baseline consultations, 43% of all men with two or more consultations tested at least every 12 months, whereas 6% tested at least every 6 months. Based
on these results, we may conclude that a frequent repeat of testing is low, especially considering that the non-governmental organisation SOA AIDS Netherlands advises MSM to test half-yearly and even every three months when being at higher risk, for example being HIV-infected or practicing high-risk behaviour [22]. These recommendations were established in co-operation with STI clinics and based on considerations of strategy and logistics, among others (personal communication W. Zuilhof, SOA AIDS Netherlands). The main rationale for frequent testing is to detect and start treating HIV in an early phase to limit viral load and to prevent HIV transmission, since HIV is most infectious during early infection. Currently, the Amsterdam STI clinic tends to advise half-yearly testing to a selected group based on risk behaviour (personal communication T. Heijman, Amsterdam STI clinic). It is not clear to what extent standardised testing advice is given to MSM at other Dutch STI clinics.

The percentage of MSM repeatedly testing for STI at the Amsterdam STI clinic during years two through four was much lower than in the first year of the study. This decline with increasing follow-up time gave us new insights into the percentage of MSM that continues to return to the STI clinic. In prior Dutch studies, testing frequencies were self-reported during surveys. Our results suggest that self-reported percentages from surveys are likely to overestimate true testing behaviour. For example, a Dutch survey of lesbian women, homosexual men, bisexual men and women and transgender (Rutgers WPF) asked in 2013 if a person had tested for STI in the past 6 or 12 months, reporting that 37% of HIV-negative MSM were tested in the past 12 months and 21% in the past 6 months [23]. A survey among MSM (the Schorer monitor 2011) included a question about repeated STI testing. Of the HIV-negative MSM who tested in the past two years, 27% reported repeated yearly testing and 19% reported half-yearly testing [24]. However, differences in study populations and testing outside STI clinics might explain the discrepant findings.

The low percentage of MSM testing biannually for STI at the STI clinic could suggest that MSM are poorly motivated to return regularly for a subsequent STI test, or they make an individual estimation of their risk and need to test. Before drawing firm conclusions, more insight is needed into the STI positivity of frequent versus less frequent testers and into their testing behaviour outside STI clinics. It could well be possible that to a large extent, testing frequency is a response to high-risk behaviour among MSM, i.e. MSM seek testing mainly when they perceive themselves at increased risk for STI. In line with this hypothesis, we showed (see Chapter 3.1) that men who tested at least annually reported slightly higher risk behaviour compared to men with less frequent testing. If testing behaviour is dependent on risk behaviour and suspicion of STI, the current testing frequency could be as effective as would be the testing of all HIV-negative MSM at higher frequencies. In addition, gaining more insight into the men testing at locations other than the STI clinic would be valuable, since currently data is lacking on the proportion of MSM testing at the STI clinic as well as at the GP or other testing locations.

There are no current national guidelines on STI testing frequency in the Netherlands. Before being able to give guidance to public health services and GPs on testing advice for MSM and on whom to motivate to return frequently for testing, we should explore STI testing frequency in relation to positive STI test results. In addition to analysing the observational databases of the
STI clinic, we could use mathematical modelling to explore the effectiveness of various testing frequencies. The results from current and future studies on STI testing frequency could guide protocols on whom and how often to test for STI.

In this study we restricted our analysis to the data collected at the Amsterdam STI clinic. Amsterdam is the largest city of the Netherlands and is estimated to have a high proportion of MSM: 10% of male inhabitants [25, 26]. One may question the representativeness of Amsterdam in relation to the rest of the Netherlands. Until 2014, an individual’s consultations were not tracked within all STI clinics but only the Amsterdam STI clinic. However, a unique patient identification number has now been added to the national STI surveillance data, making it possible to track a patient at a certain STI clinic. In a couple of years, STI testing frequency could be analysed for the whole of the Netherlands to validate current findings.

HIV-infected MSM
Among HIV-infected MSM, the prevalence of asymptomatic STI is high (16%), including mostly syphilis, anorectal chlamydia, or Neisseria gonorrhoeae (hereinafter, gonorrhea) [27]. Anorectal chlamydia was the most prevalent STI, diagnosed in 7.5% of HIV-infected MSM visiting the HIV treatment centres of Amsterdam and Rotterdam in 2007 and 2008 [27]. In Chapter 3.2 it was estimated that yearly screening of HIV-infected MSM for asymptomatic anorectal chlamydia could reduce chlamydia incidence by 7% in the total MSM population. In addition, a reduction in HIV incidence was to be expected, as studies report a higher susceptibility to HIV when a chlamydia infection is present as well as higher transmissibility of HIV with a chlamydia co-infection [28-32]. However, it was shown that these effects were almost negligible in men who are treated with combination antiretroviral therapy (cART), as are most HIV-infected MSM in the Netherlands. As their HIV viral load is likely to be low, the effect of chlamydia testing on HIV incidence was assumed small in our study. Still, chlamydia screening could prevent new HIV cases each year (i.e. around 2% reduction in HIV incidence), mainly in the percentage of MSM in which cART is not fully effective or who are unaware of their HIV infection and not yet receiving cART.

Ours was the first study modelling the effects of chlamydia screening in an HIV-infected MSM population and estimating its effect on chlamydia and HIV incidence in the total Dutch MSM population. Yearly screening of HIV-infected MSM for anorectal chlamydia is not only effective in reducing chlamydia and HIV incidence, but will also prevent loss in quality-adjusted life years (QALYs) and save costs, as was shown in Chapter 3.3. In this cost-effectiveness study, we estimated the additional cost for implementing a routine STI screening at HIV treatment centres and the QALYs gained with this screening in relation to existing STI testing at the HIV treatment centres and other health care locations. We suggested that the intervention would remain cost-effective even with the addition of an anorectal gonorrhea test, particularly since chlamydia and gonorrhea diagnostics can now be done by the same test, and a decline in costs for diagnostics is expected in the coming years. On this basis we advised implementation of an anorectal chlamydia and gonorrhea test for MSM consulting HIV treatment centres throughout the Netherlands.
Adding a new intervention to an existing consultation protocol might not be as easy as it may seem at first glance. First, the logistic procedure needs to be worked out for sampling, diagnostics, feedback of the results, and treatment. A procedure for sampling and diagnostics was successfully piloted in a study by Heiligenberg et al. in two HIV treatment centres [27]. In this pilot study, diagnostics took place at routine visits to the HIV treatment centre, where MSM were offered an STI test for which they were requested to self-collect an anorectal swab. If a person tested positive for an STI, he was referred to an STI clinic, often located at a municipal health centre, for further testing, treatment, counselling, and partner notification. If this procedure could be introduced in all other Dutch HIV treatment centres, the logistic hurdle could be surmountable. Secondly, the cost of the procedure needs to be covered. The cost for STI diagnostics will be charged at the hospitals to which the HIV treatment centres are attached. We explored the possibility of expanding the current fee for an HIV consultation, which is covered by the health insurance companies, to include the cost of STI tests for MSM. In theory it is quite straightforward and simple to add the cost of an STI test to an existing care product, once you have the approval of the health insurance companies. In practice, however, individual HIV treatment centres have different agreements with different health insurance companies. These agreements are often made at hospital level, where costs are spread out over several health departments within the hospital. Therefore, adjusting the cost for a HIV consultation will have consequences for the cost charged to other hospital departments as well. New agreements with the health insurance companies would need to be made, not only on the coverage of a HIV consultation, but also on other affected departments. This is a very time-consuming process which has to be conducted by the hospitals themselves. After the diagnostics, all further STI testing, treatment, counselling, and partner notification would take place at the STI clinic, and related costs would be covered by the STI clinics at the municipal health centres. As these clinics are financed by the National Ministry of Health, Welfare and Sport to focus on high-risk populations, no specific problems are foreseen with this last financial hurdle. However, this example illustrates that implementation of an evidence-based intervention can be difficult, taking years to implement.

HCV SCREENING IN THE GENERAL DUTCH POPULATION

Based on studies in serodiscordant heterosexual couples, sexual transmission of HCV has been considered inefficient and testing of sexual partners of HCV-infected individuals not advised [33]. Since 2000, however, acute HCV infections have been increasingly reported among MSM, in whom they are predominantly sexually transmitted [34]. HCV infection may be defined as an STI among MSM in the Netherlands, and therefore was included in this thesis as an important target for interventions among HIV-infected MSM, since currently most HCV incident cases are reported in that population [35].

In Chapter 4.1, we calculated the Dutch HCV prevalence at 0.30% (95% CI: 0.05-0.55%), based on a national seroprevalence study conducted in 2006-2007. However, as data on specific risk factors
for HCV were often missing, we questioned how well the study represented the main high-risk populations of HIV-infected MSM and IDU, and whether or not the overall population estimate might be skewed. Therefore a second estimation was derived from the data of several studies of specific HCV high-risk populations as well as data from the above-mentioned prevalence study. This second, more extensive effort yielded a Dutch HCV seroprevalence of 0.22% (min 0.07%, max 0.37%) (Chapter 4.2). The two estimated seroprevalence rates are rather similar. That the use of group-specific data did not increase the overall prevalence could be explained by the small size of high-prevalence groups like HIV-infected MSM and IDU relative to the large high-prevalence migrant population and the general Dutch population, which is at low risk for HCV infection (Chapter 4.2: table 4.2.1).

These two HCV prevalence studies have added value over an estimation of the HCV prevalence that dated from 2004 [36]. Not only could population sizes be estimated more accurately and new HCV data included, but we also took into account that risk groups have changed over the years. For example, in the Netherlands, new HCV infections are predominantly reported among HIV-infected MSM, whereas the number of new infections among people using drugs is very low [35, 37]. Despite the high percentage of acute HCV in HIV-infected MSM, migrants born in HCV-endemic countries form the population with the largest absolute number of chronic HCV infections, as shown in Chapter 4.2. This indicates that not only HIV-infected MSM but also first-generation migrants are important populations for selective HCV screening. Now that direct-acting antivirals agents (DAAs) can inhibit HCV and the expected growing burden of HCV-related disease, testing and treating for HCV have become even more important. Treating HCV infections in MSM could also have an impact on the prevalence of chronic HCV and might prevent new HCV cases, since HCV transmission is high among MSM [37]. Transmission of HCV appears to be low between migrants in the Netherlands [38, 39]. Current clinical trials are focussing on newer and even more effective DAAs, and on administering DAAs to HIV-infected persons who are also being treated with cART [40].

In the Netherlands, when entering a HIV treatment centre, HIV-infected MSM are screened for HCV antibodies. If they test antibody-positive, an additional HCV-RNA test will follow according to HIV treatment guidelines (www.nvhb.nl/richtlijnhiv). At all follow-up visits, HIV-infected MSM are tested for elevations of the liver enzyme alanine aminotransferase (ALT). No national guidelines exist on when to retest for HCV at the HIV-treatment centres during follow-up consultations, but clinicians often test for HCV when new or unexplained rises in ALT occur and especially when rises accompany high-risk sexual behaviour or a concomitant STI. This approach is in line with the recommendations of the Centres for Disease Control and Prevention (CDC) [41]. European recommendations are to screen HIV-infected MSM at risk for contracting acute HCV infection at a 6-month interval for ALT elevations and annually for the presence of anti-HCV antibodies [42]. This strategy was estimated to be cost-effective and to extend life expectancy [43].

As with HCV testing at HIV treatment centres, no guidelines exist for HCV testing at STI clinics in the Netherlands. In the national STI surveillance data of 2013, most STI consultations among HIV-infected MSM were reported by the Amsterdam STI clinic, where all HIV-infected MSM are tested
for HCV antibodies at every visit if previous testing found them antibody-negative. The 2013 surveillance data showed that, over all Dutch STI clinics, 56% of known HIV-infected MSM and 39% of MSM newly diagnosed with HIV were tested for HCV during their visit at the STI clinic. The percentage of HIV-infected MSM tested for HCV could be slightly higher if the known HCV cases could have been subtracted from the denominator. This was not possible, since it is not reported when someone has previously tested HCV-positive and is therefore not tested at the current visit. The HCV positivity rate among all HCV-tested HIV-infected MSM was 1.4% among known HIV-infected MSM and 0.8% among MSM newly diagnosed with HIV (SOAP 2013). In the Amsterdam STI clinic, 777 HIV-infected MSM were retrospectively tested for the presence of both HCV antibodies and HCV RNA: 12% tested positive for HCV antibodies and/or HCV RNA. Of the HCV/HIV-infected MSM, 15% were defined as having a recent HCV infection (i.e. anti-HCV negative and HCV RNA positive) [44]. Data from the Schorer monitor in 2011 showed that the reported HCV positivity among HIV-infected MSM tested in that year for HCV was 4%, whereas among HIV-infected MSM that were tested longer ago, the HCV positivity was 17% [24]. With current development of DAAs, one should consider intensifying the current HCV testing strategies for HIV-infected MSM at HIV treatment centres and STI clinics, since new HCV cases are predominantly reported in this subpopulation, and treatment might act as a prevention strategy [45]. To intensify, we first need to gain insight into current testing policies at HIV treatment centres and STI clinics and to explore the proportion of HCV infections that are missed with current testing rates. Mathematical modelling could then be used to estimate the impact of different HCV testing rates on HCV incidence and prevalence, and subsequently to estimate the related cost-effectiveness ratio.

In the Netherlands, no systematic HCV screening takes place among migrants, although several pilot studies have evaluated screening approaches among certain migrant subpopulations [46, 47]. We support the recommendations made in 2011 by Urbanus et al [38] that first-generation migrants from HCV-endemic countries should be screened at least once after entering the Netherlands, preferably combined with HBV screening. An effective strategy is needed to identify these underdiagnosed individuals in the general population. One possibility could be to add HCV screening to the screening of pregnant women which takes place during the first midwife appointment (< 13th week of the pregnancy) [48]. At that time, pregnant women are tested for syphilis, hepatitis B and HIV according to the opting-out principle (i.e. after being provided with information, they are tested unless they explicitly state that they do not wish to participate). Almost all pregnant women in the Netherlands participate in this infectious disease program [48]. It was estimated that adding a HCV test to all women eligible for the antenatal screening would not be cost-effective, whereas adding a HCV test to the screening of a selected population of pregnant women born in high-endemic countries appeared borderline cost-effective [49]. Even if the test were added, it would not benefit men or the women not reached with antenatal screening. Therefore, the question remains how to reach all first-generation migrants. A solution would be a national screening program targeting migrants from HCV-endemic countries, which is in line with recommendations of the World Health Organization (WHO) [50]. Implementing such a program is being considered by the Health Council of the Netherlands. A cost-effectiveness study,
estimating the number of QALYs that could be gained and the related cost to gain a QALY, could increase the chance for program approval.

**CONCLUSION**

The studies presented in this thesis have explored a range of strategies to control the STI epidemic. Significant progress has been made in STI control in the Netherlands, with vaccination and active testing policies. Future studies will show what the impact of HPV vaccination will be on HPV prevalence in the vaccinated and unvaccinated population. In addition, STI control strategies are well organized in the Netherlands, but there remains room for improvement, such as expanding the target population for HPV vaccination to include MSM, and increasing STI testing coverage among HIV-infected MSM. Furthermore, to control spread and disease burden of infections, additional screening efforts are needed among at-risk populations that do not present themselves for testing, notably HCV screening of migrants born in HCV-endemic countries.

We may conclude that epidemiological studies, including mathematical modelling and cost-effectiveness studies, contribute greatly to the development of new interventions and to the evaluation and optimisation of existing interventions designed to control the STI epidemic in the Netherlands.
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