Interventions for STI control: vaccination and testing
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Introduction
Sexually transmitted infections (STI) continue to cause significant morbidity and mortality in the population, with increasing numbers of recorded diagnoses at STI clinics in the Netherlands over the past decade [1]. Interventions are necessary to reduce transmission and spread of STI. Currently, the main interventions are based on vaccination (i.e. primary prevention) and testing and treatment (i.e. secondary prevention). In addition, behavioural interventions such as promoting condom use and safe sex practices are important. In this thesis we will focus on the interventions of vaccination and testing.

STI VACCINATION

Vaccination is a prevention strategy that can decrease incidence of an infection and may even eradicate an infection from the population, as was achieved for smallpox [2]. A decline in incidence will in the end reduce morbidity and mortality by preventing transmission of infectious diseases. Unfortunately, effective vaccines are currently available for only two STIs: infections with the hepatitis B virus (HBV) and the human papillomavirus (HPV). Both types of vaccines have been implemented in the Dutch national immunisation program (www.rivm.nl/Onderwerpen/R/Rijksvaccinatieprogramma).

To allow an immunisation program to be effective, it is important to map current needs for vaccination an identify populations who will benefit most from vaccination. Acceptance of vaccination is equally important to reduce the spread of infection and the prevalence of related morbidity. Limited acceptance could lead to suboptimal coverage rates in the population, as was observed upon the introduction of HPV vaccination for girls in the Netherlands in 2009 [3]. When coverage is low, effectiveness of a vaccine to prevent infection and morbidity will still be high for the vaccinated population, but effectiveness at the population level could be less optimal. Epidemiological studies are necessary to assess effectiveness of a vaccine in the general population. Important questions to be answered include: ‘At what moment in time are effects among vaccinated persons visible?’ ‘Does the observed effect size of vaccination on the prevention of infection and morbidity equal the predicted effect size estimated from measured efficacy of the vaccine during clinical trials?’ ‘Are there indirect protective effects among the unvaccinated population?’

Hepatitis B vaccination

Chronic infection with HBV can cause cirrhosis and cancer of the liver. Without effective treatment or liver transplantation, this can be fatal. In high endemic countries, perinatal transmission of HBV by the chronically infected mother to the neonate is the most common route [4]. In low endemic countries, including the Netherlands, most HBV infections are transmitted through unprotected sexual contact or sharing of injecting equipment among injecting drug users (IDUs) [4], although transmission in IDUs is nowadays hardly seen in the Netherlands [1].
HBV infection can be prevented by vaccination. A safe and effective vaccine against HBV became commercially available in 1982. Since 1983, the Netherlands has offered vaccination to specific subpopulations at risk for HBV (among others, haemophilia and haemodialysis patients, persons with occupational risk or behavioural risk, and infants born to HBV-positive mothers) [5]. In the years following the introduction of HBV vaccination, several changes have been applied to the HBV immunisation program [5]. One example of a major revision was the inclusion of universal HBV vaccination of all infants in the Dutch national immunisation program from August 2011 onwards. This revision followed an evaluation by the Dutch Health Council of the effectiveness and cost-effectiveness of expanding the selective vaccination program targeting high-risk groups, including infants at risk, to offer universal vaccination of all infants [5]. In addition, defined target populations at-risk for HBV and eligible for vaccination were often revised, adding or subtracting subgroups. All these revisions led to the current Dutch HBV-vaccination program which consists of: 1) universal HBV vaccination in the Dutch national immunisation program of all infants; 2) targeted HBV vaccination of men who have sex with men (MSM) and commercial sex workers and their clients; and 3) HBV vaccination of drug users attending drug treatment services.

Monitoring the effects of HBV vaccination is important. As there is still some uncertainty about the duration of protection after vaccination, the long-term impact of HBV vaccination requires attention [6]. In addition, for policy making as to HBV prevention, it is important to continue obtaining insight into the effectiveness and cost-effectiveness of current HBV vaccination programs. For example, changes in the epidemiology of HBV could make current subpopulations targeted for HBV vaccination less relevant and give rise to new at-risk populations.

**Human papillomavirus vaccination**

A relatively new vaccine is the vaccine protecting against HPV. HPV infection is a frequently occurring STI caused by 170 identified subtypes that are designated high-risk and low-risk in oncogenicity [7]. It has been estimated that 80% of the population will be infected with HPV in their lifetime. When caused by a high-risk HPV type, 80-90% of these infections will be spontaneously cleared within three years [8]. For low-risk HPV infections, the percentage is even higher, i.e. 90% or more [8]. A persistent HPV infection can cause symptoms. The most common symptoms caused by persisting infections with low-risk HPV types are warts on hands and feet. Warts can also be located anogenitally. These anogenital warts are predominantly caused by HPV subtypes 6 and 11 [9, 10]. A rare complication of a persistent infection with high-risk HPV types, which can appear after 20-30 years, is cancer [11]. The most common HPV-related type of cancer is cervical cancer in women. The main HPV types associated with invasive cervical cancer are HPV-16 and -18, detected in approximately 61% and 10%, respectively, of all cervical cancer cases [12]. In addition to cervical cancer, persistent high-risk HPV infections can also cause vulvar, vaginal, anal, penile and oropharyngeal cancer [13].

Currently, there are two approved HPV vaccines, the bivalent vaccine Cervarix® targeting HPV-16/-18 (approved for females) [14], and the quadrivalent vaccine Gardasil® targeting HPV-6/-11/-16/-18 (approved for males and females) [15]. Both vaccines are highly effective (98%) in the
protection against high-grade squamous intraepithelial lesions (HSIL), i.e. precancerous changes of the cells on the surface of the cervix which may be associated with malignancy of the cervix [14, 15]. There is evidence for additional vaccine-specific cross-protection against high-risk HPV types not included in the vaccine [16-18]. Among women negative for HPV-16/-18, a significant efficacy against HPV-31/-33 was seen with Cervarix® [18] and against HPV-31 with Gardasil® [16]. In addition, Gardasil® is highly effective against anogenital warts caused by HPV-6 and -11 [19]. Recently, studies suggested that Cervarix® likewise has a moderate protective effect against these warts [20, 21]. At the end of 2013, results were presented for phase III trials with a 9-valent HPV vaccine targeting HPV-6/-11/-16/-18/-31/-33/-45/-52/-58, showing an efficacy of 97% against HSIL among 16- to 26-year-old women [22].

From 2010 onwards, the Netherlands implemented HPV vaccination with the bivalent vaccine (Cervarix®) in the national immunisation program. Until 2014, all girls aged 12 years were offered vaccination in a three-dose schedule (i.e. at 0, 1, and 6 months) [23]. From January 2014 onwards, this protocol was reduced to a two-dose schedule (i.e. at 0 and 6 months), since the immune response after two doses in women aged 9 to 14 years was found to be as good as the immune response after three doses in women aged 15 to 25 years [24]. The age of 12 was chosen since the incidence of HPV infection drastically increases when individuals become sexually active. A catch-up campaign was organised in 2009 for all girls from 13 to 16. The HPV vaccine does not substitute for the existing cervical cancer screening program, in which all women from the age of 30 onwards are invited for a cervical smear at least every 5 years to screen for abnormal cytology.

Monitoring the impact of HPV vaccination in the vaccinated and unvaccinated population is important. Along with the intended effects of reduction in incidence and prevalence of HPV vaccine types and a subsequent decline in premalignant lesions and cancer, unwanted effects might also occur. It is hypothesised that oncogenic non-vaccine HPV types could take over the ecological niches created by the eradication of vaccine HPV types, but no such ‘type-replacement’ has thus far been reported [25]. Another hypothesised consequence of vaccination is ‘unmasking’, a phenomenon in which non-vaccine HPV types become apparent in disease when vaccine HPV types (those types which are currently assigned as main causal types in cervical cancer cases) are removed and hence stop ‘masking’ the non-vaccine HPV types [26]. Since the above-mentioned effects in the vaccinated and unvaccinated population may take many years to become visible, continuation of current post-vaccination epidemiological studies is necessary. Likewise the long-term effects of the two-dose schedule will be important to monitor [27], as evidence is based on the level of immune response up to a maximum of four years post-vaccination [24, 28].

Vaccines in development
Vaccine development is often a complex and expensive process. It can take over 20 years before a vaccine is developed and confirmed to be safe and effective [29]. For example, in November 1986 the first HIV vaccine clinical trial took place, a first step towards the development of an HIV vaccine [30]. Today, nearly 30 years later, HIV vaccine development is still ongoing [31]. Moreover, there have been, and there are still, many ongoing efforts to develop vaccines against herpes simplex
type-2 [32], *Chlamydia trachomatis* [33, 34], *Trichomonas vaginalis* [35], and *Neisseria gonorrhoeae* [36], as well as hepatitis C (HCV) [37], which recently emerged as an STI among HIV-infected MSM [38]. In addition, syphilis would be a candidate for which to develop a vaccine [39]. Development of effective and affordable vaccinations against one or more of these STI would be a major contribution to further control of STI.

### STI TESTING

Detecting and treating an STI at an early stage of infection can prevent complications. In addition, STI testing is important in STI control, as treatment can clear infection or could reduce infectiousness in chronic STI like HCV and HIV. In the Netherlands, the general practitioner (GP) is the main site where each year approximately 90,000 STI are detected and treated [1, 40]. In addition, persons with STI-related symptoms or persons at increased risk have the opportunity to test for STI at an STI clinic [41]. In the Netherlands, STI clinics are mostly located at public health services and are relatively easy to access, since care, including treatment, is anonymous and free of charge for target populations. Target populations are populations at increased risk for STI acquisition. The following target populations are currently identified: persons reporting STI-related symptoms, persons being notified or referred for STI testing, young people under the age of 25 years, MSM, commercial sex workers, persons originating from an area considered to be HIV/STI-endemic (Surinam, Netherlands Antilles including Aruba, Africa, Latin America, Asia and Eastern Europe [42, 43]), persons having had three or more sex partners in the past 6 months, and persons with a partner from one of these risk groups [1]. In addition to the GP and STI clinics, other medical settings, for example departments of dermatology, urology or gynaecology, also carry out STI tests.

**Strategies to reach people with asymptomatic STI**

It is likely that persons with STI-related symptoms present themselves at a GP or STI clinic. However, a large proportion of STI remain without symptoms [44, 45]. Therefore, persons with high-risk sexual behaviour are advised to test on regular basis at a GP or STI clinic (http://www.soatest.nl). Since only a fraction of persons at high risk without symptoms will test on their own initiative [46], strategies are needed to motivate them to test. Examples of strategies to increase testing for asymptomatic infections include notifying sexual partners of individuals diagnosed with an STI, increasing knowledge and awareness of individual risk, but also screening of populations at risk.

By screening for STI, we refer to the testing of individuals who are not directly seeking any health care because of STI-related problems. Screening was defined by the CCI Conference on Preventive Aspects of Chronic Disease in 1951 [47] as: ‘The presumptive identification of unrecognised disease or defect by the application of tests, examinations, or other procedures which can be applied rapidly. Screening tests sort out apparently well persons who probably have a disease from those who probably do not. A screening test is not intended to be diagnostic. Persons with positive or
suspicious findings must be referred to their physicians for diagnosis and necessary treatment.

Various screening strategies exist. One can screen on a large-scale basis, making no selection of specific population groups (i.e. mass screening), or one can apply screening only to population groups at increased risk for infection (i.e. selective screening or targeted screening) [48]. An example of a selective screening program in the Netherlands was the Chlamydia Screening Implementation (CSI) program which started in 2008 [49]. The goal was to trace and treat chlamydia infections among persons younger than 30 years. All 16- to 29-year-old men and women of Amsterdam and Rotterdam were invited by letter to be screened for chlamydia, and in South Limburg persons with high risk were selected. Unfortunately, the overall program was not found to be cost-effective due to low participation and positivity rates, and was stopped in 2011 [50]. However, the stricter selection of high-risk populations in South Limburg led to higher positivity rates [51], which could have led to lower cost per quality-adjusted life years (QALYs) gained. That a stricter selection of populations could improve cost-effectiveness was shown in a study estimating the cost-effectiveness of adding HCV screening to the existing antenatal national screening program. A HCV screening program selecting all pregnant women was likely not cost-effective, whereas a HCV screening program selecting first generation non-Western women showed a modest cost-effectiveness [52].

Another screening strategy is case-finding. This type of screening occurs in a clinical setting when patients visit their physician (or other health provider) for general consultation or unrelated problems, and the physician takes the opportunity to request one or more routine screening tests. With case-finding, the chance that a person returns for follow-up after a screening test is highest. An example of case-finding in the Netherlands is the testing of pregnant women by a midwife or obstetrician/ gynaecologist for HBV, syphilis and HIV to prevent mother-to-child transmission [53]. Another example of case-finding is the testing of persons visiting an HIV treatment centre to detect co-infections. HIV-infected persons are seen twice a year at the HIV treatment centres and are tested at entry for hepatitis A, B and C and once-yearly for syphilis (http://www.nvhb.nl/richtlijnhiv/). Case-finding has been referred to as 'opportunistic screening.'

It should be noted that in the literature and in spoken language, the words ‘testing’ and ‘screening’ are often used interchangeably. Some people define STI screening as testing for STI in a whole population or subgroups, regardless of symptoms or risky behaviour. Others define STI screening as testing people without STI symptoms, but with a certain risk profile. Conversely, screening asymptomatic people is often equated with testing, and the definition of case-finding is often mixed with the overall definition of screening. The overlap in definitions between testing and screening makes it hard to make a clear distinction between them. In this thesis, ‘testing’ is used for persons who visit a health care facility with the specific request for an STI test. For example, they want to test for STI because they have STI-related symptoms or practiced unsafe sex. The term ‘screening’ is used when a population is actively approached for an STI test, but its individuals did not ask for testing on their own initiative.
STI testing strategies for hard-to-reach and hidden populations

There are populations at risk for STI but hard-to-reach since they are not visiting a clinician on their own initiative, and are not regularly seen at any other health care facility. These populations might be hidden. Hidden populations lack a sampling frame, a list of all members in the population [54]. It is hard or sometimes impossible to reach a hidden population, because of its small size or the difficulty of locating its members. The difficulty of locating members could be caused by the sensitive nature of the behaviours in the population (for example, among men who have sex with men, drug users or clients of commercial sex workers). In addition, sometimes members of the target population are difficult to distinguish from members of the general population because the group is defined on basis of behavioural aspects (for example, persons with multiple sex partners). Nevertheless, it is important to try to map and reach the hard-to-reach and hidden populations to prevent STI transmission, morbidity and even mortality. For example, HIV and HCV infections can be fatal when remaining without treatment.

Epidemiological studies offer opportunities to map the hard-to-reach and hidden populations at risk and to estimate population size. In the last decade, the internet has offered new opportunities to reach and test them. Healthcare workers can use forums, chat rooms and social networking sites to discuss sensitive subjects. These sites can also be used to publicise and promote STI testing by health care providers. In addition, websites provide the opportunity to reach hidden and hard-to-reach populations and can offer tests for STI (e.g. by providing the possibility of online ordering a test package for testing at home or ordering home-based collection materials which can be sent to a laboratory for testing). Outreach activities are also used, as when healthcare workers visit locations frequented by high-risk populations to offer them a test on site. Examples of such locations are places that attract subgroups of MSM like bars, ‘cruising areas’, and saunas, but also locations for commercial sex workers, like ‘red light’ districts, or for IDUs, like ‘shooting galleries’.

STUDY DESIGNS TO MEASURE EFFECTIVENESS OF INTERVENTIONS

Several strategies exist to control the STI epidemic, as mentioned above. The decision to implement an intervention is based on its predicted effectiveness and cost-effectiveness. A randomised controlled trial (RCT) is often considered as the most optimal study design to measure efficacy of an intervention. In an RCT, patients are randomised to receive or not to receive the intervention. Randomisation ensures that, on average, all other possible prognostic factors, but also unknown factors, are equally distributed between the two groups. Thus, any significant difference between groups in the outcome event can be attributed to the intervention and not to some other known or unknown factor. The downside of a RCT is that it is not always feasible, appropriate or ethical to perform, and is often expensive and time-consuming. In addition, the intervention is given under artificial conditions to a restricted population (i.e. persons meeting the inclusion and exclusion criteria to participate) which will often differ from real life. Other limitations are that RCTs usually do not include long-term endpoints such as survival and often involve sample sizes or study periods that are insufficient to detect rare adverse effects, endpoints which can
be highly relevant. An alternative design is a mathematical model. Modelling studies provide the opportunity to simulate different scenarios and to estimate the effect per scenario without needing large study populations, budgets, or having ethical difficulties. However, since models are simple representations of real life, they rely on simplifying assumptions. Models are often parameterised on data such as prevalence or the number of partners in the last year. However, these data are not always available for the specific subpopulations or are too difficult to measure in real life. In such cases, the best available alternative data is used, or parameters are based on expert opinion. When interpreting model outputs, the assumptions of the model and the data where the model is parameterised should always be kept in mind.

Once an intervention has been implemented, additional observational studies can be used to gain insight into its short- and long-term effectiveness and cost-effectiveness, especially since effectiveness measured in RCTs or modelling studies could differ from actual effectiveness in the general population. As new risk populations may arise and current target populations may become less important after implementing interventions, it is important to frequently evaluate existing interventions, and if necessary to revise them to ensure they remain effective and cost-effective. In addition, unfavourable events that may occur, e.g. resistance to therapy, diagnostic escape mutants, side effects of vaccination and changes in the STI epidemic, may lead to the need for new interventions.

In this thesis, two main observational study designs are used to observe the effectiveness of STI interventions: cohort and cross-sectional. Both designs have advantages and disadvantages in gaining insight into effectiveness [55]. Briefly, a cohort study can be used to describe the incidence and natural history of STI. Participants might be exposed to a certain intervention, for example STI testing, and are followed over time. Comparing these exposed participants to non-exposed participants makes it possible to assess the effectiveness of the specific intervention. Since cohort studies include sequential measurement points over time, one can distinguish causes from effects. A prospective cohort study is preferred, but one can consider using a retrospective cohort design, which is cheaper and quicker to perform. In analysing cohort studies, confounding variables should be taken into account. In addition, bias can occur due to subject selection and loss to follow-up. Cross-sectional studies are adequate when the main goal is to determine prevalence. Cross-sectional studies are less time-consuming than RCTs or cohort studies and allow analyses of multiple exposures and outcomes. Unfortunately, since measurement in an individual takes place at a single moment in time, it cannot differentiate between cause and effect. Therefore, the evidence for a causal effect or association is less strong compared to effects detected in cohort studies or RCTs.

OUTLINE OF THIS THESIS

This thesis describes and evaluates vaccination and testing interventions for STI control that target risk groups in the Netherlands (see also table 1.1). Chapter 2 focusses on HPV in a highly sexually active young population. In 2009, we set up a multiple-round cross-sectional study (PASSYON,
Papillomavirus Surveillance among STI clinic Younsters in the Netherlands) to monitor the effects of HPV vaccination, which was introduced that same year, on prevalence among young STI clinic attendees. STI clinic attendees are at high risk for HPV and are expected to have a high HPV positivity rate. The outcomes of the baseline measurement, taken when the study population was still unvaccinated, are described in Chapter 2.1.

Testing for HPV DNA is an expensive method to detect a current anogenital HPV infection. An alternative and considerably cheaper method could be HPV antibody detection. To evaluate if serology would be a reliable method for monitoring the effect of HPV vaccination, we assessed in Chapter 2.2 the associations between HPV DNA and HPV antibody positivity using data from the PASSYON study.

An infection or coinfection with chlamydia is common among young female STI clinic attendees. In Chapter 2.3 we investigated whether a chlamydia infection increases the risk of acquiring an HPV infection among young females and if a co-infection with chlamydia interferes with the clearance of HPV. For this study we used data from the CSI program, a longitudinal cohort.

The Dutch decision to vaccinate against HPV was driven solely by the need to prevent cervical cancer. However, anogenital warts often occur in sexually active persons, potentially leading to physical and emotional distress. An HPV vaccine protecting against wart-specific HPV types as well as oncogenic types could benefit this population. To gain insight into the impact of having anogenital warts, we investigated their effect on emotional and sexual well-being among persons presenting with such warts at their visit to the STI clinic. This study is described in Chapter 2.4.

In Chapter 3, we focus on MSM. MSM have a high STI positivity rate, and HIV is still spreading among MSM in the Netherlands. The MSM population is therefore an important target group for STI control. To give guidance on STI testing frequency, insight into current testing behaviour and test results is required. Chapter 3.1 describes the current testing behaviour of HIV-negative MSM attending the STI clinic of the Public Health Service of Amsterdam. In the subsequent two parts we focus on HIV-infected MSM. STI co-infections are often present in HIV-infected MSM and might enhance HIV transmission. However, a large part of these infections remain undetected due to the absence of symptoms and limited testing. Chapter 3.2 analyses the effect of implementing routine chlamydia screening on the spread of chlamydia and HIV within this population, and in Chapter 3.3 the cost-effectiveness of such an implementation is estimated.

Chapter 4 describes the prevalence of hepatitis C virus (HCV) infections within the general Dutch population. The first part of the chapter (Chapter 4.1) uses a cross-sectional nationwide study to estimate the HCV prevalence. The second part (Chapter 4.2) uses these results as well as prevalence data from other Dutch studies that target specific high-risk populations to derive a more robust estimation and provide insight into the size of subpopulations with HCV infections in the Netherlands. Such data are needed to inform screening programs.

Chapter 5 concludes with a general discussion and summarizes the work described in this thesis.
Table 1.1. Overview of characteristics and data sources used in this thesis.

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Data sources</th>
<th>Study population</th>
<th>Study design</th>
<th>Study period</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>PASSYON (PApillomavirus Surveillance among STI clinic YOungsters in the Netherlands)</td>
<td>STI-clinic attendees aged 16-24 years</td>
<td>Cross-sectional</td>
<td>2009</td>
</tr>
<tr>
<td>2.2</td>
<td>PASSYON (PApillomavirus Surveillance among STI clinic YOungsters in the Netherlands)</td>
<td>STI-clinic attendees aged 16-24 years</td>
<td>Cross-sectional, repeated once every other year</td>
<td>2009 &amp; 2011</td>
</tr>
<tr>
<td>2.3</td>
<td>CSI (Chlamydia Screening Implementation)</td>
<td>Female citizens of Amsterdam, Rotterdam and selected municipalities of South Limburg aged 16-29 years</td>
<td>Controlled trial with randomised stepped-wedge implementation in three blocks</td>
<td>2008 - 2012</td>
</tr>
<tr>
<td>2.4</td>
<td>Dutch STI clinics</td>
<td>STI-clinic attendees presenting with anogenital warts</td>
<td>Cross-sectional</td>
<td>2012</td>
</tr>
<tr>
<td>3.1</td>
<td>Amsterdam STI clinic</td>
<td>HIV-uninfected MSM</td>
<td>Longitudinal surveillance</td>
<td>2008 - 2012</td>
</tr>
<tr>
<td>3.2</td>
<td>Several sources re: STI transmission, sexual behaviour, STI positivity</td>
<td>HIV-infected and -uninfected Dutch MSM</td>
<td>Modelling study</td>
<td>N.A.</td>
</tr>
<tr>
<td>3.3</td>
<td>Outcomes transmission model (Chapter 3.2) and several sources re: cost and quality-adjusted life years (QALYS)</td>
<td>HIV-infected MSM at a Dutch HIV treatment centre</td>
<td>Cost-effectiveness study</td>
<td>Target year 2011</td>
</tr>
<tr>
<td>4.1</td>
<td>PIENTER-2 study</td>
<td>General Dutch population aged 15-79 years</td>
<td>National population-based cross-sectional serosurvey</td>
<td>2006 - 2007</td>
</tr>
<tr>
<td>4.2</td>
<td>Several sources including data on HCV prevalence among at-risk populations in the Netherlands as well as results in Chapter 4.1</td>
<td>HCV at-risk populations and the general Dutch population</td>
<td>Estimate using data from PIENTER-2 and studies in subpopulations</td>
<td>Target year 2009</td>
</tr>
</tbody>
</table>
Chapter 1

REFERENCE LIST


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