Optimizing sexually transmitted infection care in men who have sex with men

OPTIMIZING SEXUALLY TRANSMITTED INFECTION CARE IN MEN WHO HAVE SEX WITH MEN:

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thinking outside the box

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CONTENTS

ZONDE ZONDER ZONDE

Er staan twee mannen, hand in hand
Een tekent een hart in het mulle zand
Met een zwierige beweging de laatste lus
Hij glimlacht en geeft hem een kus

Er liggen twee mannen, hand in hand
Na een avondje stappen in één bed beland
Een staat op, trekt zijn kleren aan
Om daarna snel naar huis te gaan

Er zitten twee mannen, hand in hand
Met peinzende gezichten aan de waterkant
Een gooit een steentje, wacht tot de rimpels zijn gedoofd
Ze gaan niet weg, de rimpels in het voorhoofd

Er lopen twee mannen, hand in hand
Een met bedroefd gezicht, zijn schaamstreek staat in brand
Zonde zonder zonde, want laten we wel wezen
Voorkomen is altijd beter dan genezen

Er zijn twee mannen, hand in hand
Beiden gebruiken ze hun gezond verstand
Ze laten hun leven niet meer verpesten
En gaan aan de slag met thuis testen

Sjef Leenen, 2021

LIST OF ABBREVIATIONS

AIDS – Acquired Immune Deficiency Syndrome
AMR – Antimicrobial Resistance
CI – Confidence Interval
CO – Change Objective
COVID-19 – Coronavirus Disease 2019
CT – *Chlamydia trachomatis*
DNA – Deoxyribonucleic Acid
GI – Gastrointestinal
GM – *Chlamydia muridarum*
GP – General Practitioner
HIV – Human Immunodeficiency Virus
HBV – Hepatitis B Virus
IM – Intervention Mapping
IQR – Interquartile Range
LGV – Lymphogranuloma Venereum
MSM – Men who have sex with men
NAAT – Nucleic Acid Amplification Test
NG – *Neisseria gonorrhoeae*
OR – Odds Ratio
PID – Pelvic Inflammatory Disease
PO – Performance Objective
SD – Standard Deviation
STIs – Sexually Transmitted Infections
WHO – World Health Organization

CHAPTER 1

General introduction

Sexually transmitted infections (STIs), including human immunodeficiency virus (HIV), are a significant cause of morbidity worldwide [1]. STIs are caused by bacteria, viruses and parasites that are commonly spread by sexual activity. STIs are among the most common communicable diseases and can have severe outcomes such as pelvic inflammatory disease (PID) and infertility in women or proctitis in men [2-4]. Worldwide, 37.9 million people are living with HIV, with 1.7 million new infections in 2018 [1]. In the Netherlands, more than 20,000 people are infected with HIV [5].

Men who have sex with men

In this thesis, we focus on men who have sex with men (MSM). MSM are one of the key populations most affected by STI (including HIV). The incidence of STIs is increasing at a faster rate among MSM than other populations [6]. This may be attributed to multiple factors, including individual sexual risk behaviors and sexual network characteristics [6, 7]. Individual behavior, such as the number of sex partners, rate of partner exchange, lack of condom use and introduction of new technologies for meeting sex partners (such as online dating apps) increases the likelihood of exposure to STIs. Sexual network characteristics are related to interconnectedness and concurrency of sex partners, facilitating STI spread [6-8]. MSM are a risk group for STIs like *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG), hepatitis B, syphilis and HIV. In the Netherlands, there were 580 new HIV diagnoses in 2019, the majority (61%) in MSM [9]. In 2019, 77% of NG cases, 93% of HIV cases and 96% of syphilis cases diagnosed at Dutch STI clinics were among MSM [10].

Bacterial STIs in MSM

Chlamydia

CT infections cause chlamydia, a disease which can occur on different anatomic locations (like other bacterial STIs): the urogenital, anorectal and oropharyngeal area. Although two thirds of CT infections are asymptomatic in MSM [11], it can cause negative health outcomes such as urethritis and epididymitis.

Lymphogranuloma venereum (LGV), which is a disease caused by a specific strain of CT is asymptomatic in only 25% of the cases and can cause more severe morbidity like proctocolitis [12]. LGV originates from CT bacterium strains L1, L2, L2b and L3 and is more invasive (i.e. gets into the submucosa tissue of the body) than more common CT strains D, E, F, G, H,

I, J and K. These LGV strains cause invasive infections and subsequent severe inflammatory responses, targeting lymphatics and lymph nodes. Anorectal LGV can be characterized by anorectal cramps, pain, bloody discharge and/or constipation, and can also lead to proctitis [11, 13, 14]. Without early treatment, the infection can cause severe lesions which may require surgery. In the Netherlands, among MSM who visited STI clinics in 2019, 10.7% (4,929/46,275) were diagnosed with a CT infection and 419 MSM were diagnosed with LGV [10].

Gonorrhoea

NG infections cause gonorrhoea, a disease which can cause urethritis and inflammation of the epididymis and prostate gland in men [4, 15]. Like CT, NG infections are also often asymptomatic in MSM [11, 16]. Next to individual health problems, increased prevalence of NG also causes a worldwide public health problem by increasing antimicrobial resistance (AMR). AMR of STIs to antibiotics has increased rapidly in recent years and has reduced treatment options. In the Netherlands, among MSM who visited Dutch STI clinics in 2019, 11.5% (5,320/46,301) were diagnosed with a NG infection [10].

Syphilis

Syphilis is caused by *Treponema pallidum* which, without treatment, can persist in the body for a long time. Syphilis progresses in four stages: primary, secondary, latent, and tertiary. Primary syphilis is characterized by a lesion and if left untreated, may be followed by secondary syphilis. The identification of syphilis infections among MSM through symptom recognition and clinical screening is challenging due to the often asymptomatic nature and short duration or poor specificity of the primary and secondary stage. Therefore, serological screening for early syphilis is important, as minor or hidden lesions can be overlooked or misdiagnosed [17]. When syphilis progresses to the tertiary stage, it can cause damage to the brain, bone marrow, heart and central nervous system, also known as neurosyphilis. MSM with previous syphilis infection are at high risk for repeated episodes of syphilis infections [18]. In the Netherlands, among MSM who visit Dutch STI clinics in 2019, 2.5% (1,150/46,128) had a syphilis infection. Of the MSM diagnosed with infectious syphilis, 19.7% had a co-infection with CT and 17.0% had a co-infection with NG [10].

Viral STIs in MSM

HIV

HIV targets the CD4 cells in the immune system, which help the body respond to infection. HIV replicates within CD4 cells and damages and destroys the cells [19]. Without effective treatment, depletion of CD4 cells will cause the immune system to become weakened to the point that it can no longer fight any infection or disease [19-21]. Acquired immunodeficiency syndrome (AIDS) is the end-stage disease of HIV, which can take 2-15 years to develop. HIV treatment consist of a combination of antiretroviral drugs that modulate the course of the disease and prevent AIDS. With effective treatment, the viral load of HIV can become undetectable and sexual transmission does not occur when the partner with HIV has an undetectable viral load [22, 23].
In the Netherlands, 164 individuals, of which 93% MSM, were newly diagnosed HIV in 2019 [10]. Among MSM, 152 HIV infections were diagnosed; a decrease compared to the number of HIV infections in 2018 (n=224) and 2017 (n=256) [10]. In 2019, 12.985 HIV positive MSM were known to be in care in of the Dutch HIV treatment centers [9].

Hepatitis B

Hepatitis B is caused by the hepatitis B virus (HBV). HBV is a blood borne pathogen which can cause an acute or chronic infection. Although most adults with acute hepatitis B do not need treatment, as the infection clears spontaneously, it is highly infectious and can be easily transmitted to others. Chronic infection, when infected individuals are positive for hepatitis B surface antigen (HBsAG) for more than 6 months, can cause cirrhosis, hepatic decompensation, or liver cancer [24, 25]. Hepatitis B is preventable by vaccination. At the Dutch STI clinics, 67 cases of infectious hepatitis B (both acute and chronic) were diagnosed, of which 47.8% among MSM. Among all MSM who visited Dutch STI clinics in 2019, 0.3% (32/9,349) had a chronic or acute hepatitis B infection [10]. Since the launch in 2002, 67,185 MSM have entered a hepatitis B vaccination programme [5, 10].

STI transmission and control

To protect public health, as well as individual health, it is important to control and prevent the spread of STIs. The potential for a pathogenic microorganism to spread can be expressed by the reproductive number, denoted R_0 (or R naught). This is the average number

of susceptible people infected by an infected individual within a population [26]. This rate is determined by:

1. β - the probability of transmission in a contact between an infected individual and a susceptible one
2. κ - The frequency of contacts in the population
3. *D* - How long an infected person is infectious

The actual value of R_0 can be calculated when the largest part of the population is (again or still) vulnerable to STIs, with the equation $R_0 = \beta \cdot \kappa \cdot D$. If R_0 is greater than 1, this means that every infected person on average infects more than one new person, which will lead to an epidemic with exponential growth. If R_0 is smaller than 1, the disease will eventually be eliminated [27].

In the next paragraphs, I will elaborate on different aspects of intervening in the three different determinants of transmission in relation to HIV/STI control in MSM (figure 1). In the following chapters, this thesis will zoom in on two of the determinants; the reduction of the probability of transmission per contact by addressing hidden HIV/STI reservoirs and decreasing the duration of infectiousness by addressing timely treatment and testing.

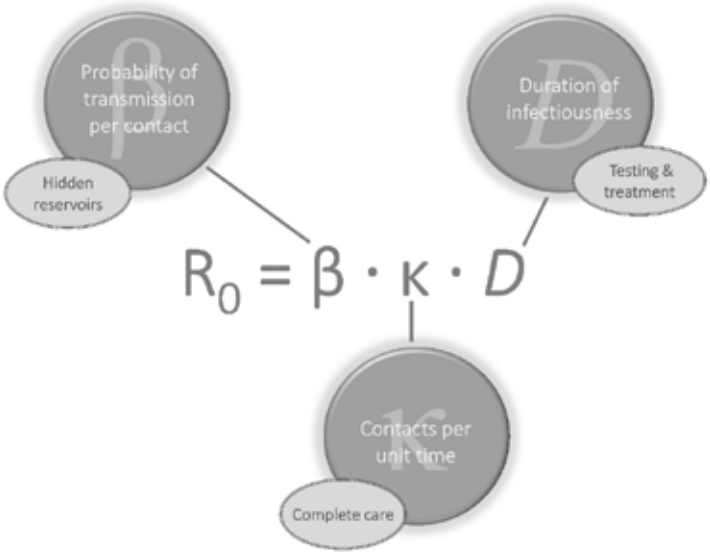

Figure 1. Reproductive rate (R_0) of infectious diseases addressing HIV/STI action points in this thesis.

β. Decrease probability of transmission per contact: hidden reservoirs

Hidden reservoirs

STIs can occur without clear symptoms, which may prevent MSM from getting tested and seeking medical care. MSM with asymptomatic infections can act as a reservoir for ongoing transmission. Infection reservoirs (e.g. untested anatomic locations within a person or untested and untreated infectious populations) are important to understand and get insight into. These reservoirs are, often unknowingly, a source of infection and re-infections; i.e. sexual transmission is estimated to be 3.5 times higher in those unaware than in those aware of their HIV infection [28]. An estimated 20% of HIV infected people living in the US are unaware of their HIV status, which causes about half of the new infections [29]. In the Netherlands in 2018, an approximately 92% of people living with HIV were estimated to have been diagnosed and linked to care [10].

Anorectal infections with CT are commonly prevalent in MSM with rates between 1-18% in STI clinic attendees [30-33]. However, these infections frequently (~50–65%) occur without reported anal sex and remain unexplained. It is important to comprehend routes of transmission in order to understand unexplained infections and reduce the probability of transmission. A theory to explain anorectal CT detection in the absence of reported anal sex involves the oropharyngeal site and the gastrointestinal (GI) tract [34, 35]. There is an ongoing debate whether humans host CT bacteria in their intestine and develop an anorectal infection via contamination from the lower GI tract [34-36]. Although there have been animal studies, which present results in favor of this theory, there are no studies done with human data who provide sufficient evidence on this subject.

Missed infections

MSM who are enrolled in healthcare do not always get tested for HIV or other relevant STIs. In a hospital setting, HIV tests are not always accompanied by STI tests [37]. For example, in a US HIV care hospital setting, STI screening in the hospital setting showed to be 2.0-8.5% [38]. The STI test practice in HIV care is likely to miss extragenital chlamydia cases, as these are often asymptomatic (36-100%) [16, 30, 39], and frequently detected in the absence of reported anal sex [16, 40-42]. Missed infections can become a reservoir for infecting other people or by infecting other anatomic locations by auto-inoculation.

D. Decrease duration of infectiousness: Testing and treatment

The number of days an infectious person has sexual contact determines the potential to expose sex partners to infection [43]. Frequent HIV/STI testing plays an important role in the control of HIV/STI transmission, because it enables timely diagnoses and treatment and shortens the duration of infection [44]. Besides optimizing outcomes after diagnosis for individuals benefit, early treatment shortens the duration of an infected individual to spread the infection, benefitting the public health by using treatment as a prevention for HIV spread [45-47]. Studies have proposed that MSM who receive antiretroviral therapy (ART) and have achieved and maintained an undetectable viral load cannot sexually transmit the virus to others, controlling transmission [45, 46, 48].

STI/HIV testing in the Netherlands

In the Netherlands, MSM are offered free of charge and anonymous HIV and STI tests at the Public Health Service STI clinics. At an STI clinic, a HIV or STI test is always accompanied by a consultation with a medical specialist or nurse, who will discuss sexual risk behaviour, sexual health and possible symptoms with the patient. In accordance with Dutch national guidelines, MSM are tested for HIV, syphilis, hepatitis B, genital, anorectal, and oropharyngeal CT and NG infections [49]. If test results are positive for one or more infections, free treatment, counselling and anonymous partner notification will be offered at the STI clinic. If MSM are not vaccinated against hepatitis B, a free vaccination will be offered. Next to in-clinic STI care, nurses and doctors at STI clinics also make an effort to reach MSM who do not visit the clinic, for example through outreach activities (e.g. visits at gay parties or sauna's, advertisements on gay websites). Getting tested at an STI clinic is optional, as MSM can also get tested at the general practitioner (GP). Depending on the type of health insurance, MSM may have to pay for the visit and tests. GPs have different HIV/STI testing guidelines compared to STI clinics, which recommend extragenital testing only based on sexual history and reported symptoms. HIV positive MSM can also get tested for STI at the hospital setting. At HIV hospital treatment centres, care providers can offer STI tests to their patients. However, there are no guidelines that recommend routine STI screening for MSM during regular HIV care visits and patients are tested only when they are considered at risk for STIs [50]. MSM without any STI-related symptoms can also request an online test (called "Testlab"), where they receive a referral letter to go to a laboratory nearby to provide a sample. However, Testlab is only available in selected regions of the Netherlands and counselling will only be provided after positive test results. Self-tests for HIV/STIs, where

patients can perform the test at home and read the test results directly, are available on the internet. For most bacterial STIs, these test have a poor performance and are unreliable [51-54]. Although there are reliable self-tests for HIV available, there are still concerns about the lack of linkage to counseling, treatment and care for self-test users who test positive [55, 56].

Infrequent HIV/STI testing

Dutch multidisciplinary guidelines recommend that MSM are routinely tested (up to 4 times a year for high risk groups). To date, not all MSM are reached with regular HIV/STI care systems or do not regularly undergo HIV/STI testing as recommended [57], leaving an unknown number of HIV and STI infections undiagnosed and untreated. Among MSM visiting Dutch STI clinics, only a minority (19%) tests as frequently as advised by national guidelines (every 6 months) [58]. An internet survey among MSM living in the Netherlands showed that 20.4% had never been tested for HIV [59].

Barriers to testing - MSM

Reasons for suboptimal testing can be attributed to different in-person and environmental factors. Among MSM, several personal barriers to HIV/STI testing have been identified in previous studies, including expected stigma from healthcare providers or laboratory staff, fear of a positive test result and its consequences, lack of time or motivation to attend care, privacy concerns (e.g., fear of being recognized at the STI clinic by other people), low-risk perception, or lack of motivation to be tested [60-64]. Next to personal barriers to testing, environmental barriers may play a role, which prevents MSM from receiving HIV/STI care. For example, stigma from their social network or availability of HIV/STI care in their region. To provide the best possible care, and reach those who currently do not get tested, it is important to assess these barriers. When knowledge about barriers is acquired, testing can be optimized by removing or lowering these barriers.

Barriers to testing - care providers

MSM are not the only ones who might need to overcome barriers to get tested. Healthcare providers may have to overcome barriers from their side that prevent them from offering HIV/STI tests to their MSM patients. Barriers are related to guidelines restrictions, competing medical priorities and professionals' uncomfortable feeling when discussing patients' sexual practices and lack of HIV/STI expertise [64, 65]. To lower the burden on care providers in offering sexual healthcare, it is important to gain insight in these barriers and their struggles in offering HIV/STI testing in daily practice.

Interventions targeting the duration of infectiousness are interventions focused on (timely) testing and treatment of infected individuals or populations, such as screening programs or online HIV/STI tests. Surveillance and identifying high-risk population subgroups can give insight in understanding local epidemics [66], including sources of new infections over time, and the behavioural and biological factors driving epidemic spread. Targeted HIV programming based on the local situation and epidemiology may be an effective approach to reducing HIV incidence [67].

k. Reducing contacts per unit time: providing complete care

In order to reduce the number of contacts an infectious person has per unit of time, sexual healthcare should not only be focused on timely HIV/STI testing, but also on counseling, partner management and adherence to treatment guidelines. Counseling can include providing information on safe sex, PrEP, Chemsex, sexual health problems, or stigma-management strategies. Partner management involves identifying sex partners, notifying them about their exposure to HIV/STIs and, if necessary, providing counseling and treatment [68]. Notification and treatment of infected partners reduces the likelihood of re-infecting a treated index patient [69]. It may also expose asymptomatic infected individuals, who otherwise do not seek care. Poor treatment adherence can lead to multidrug resistance HIV or STI strains [70, 71]. Infected individuals who do not adhere to the treatment guidelines can still be infectious and thereby spreading HIV/STI when having sexual contact during the treatment period.

For MSM who are not reached with regular HIV/STI care, additional efforts are needed to reach them in order to reduce HIV/STI transmission and improve public health. Despite considerable efforts to develop interventions that can reduce sexual risk behavior, behavior change remains a challenge. Research has demonstrated the need for theory-based development of interventions [72, 73] thereby including representatives of the identified target populations, and involve them in design, implementation and evaluation for successful and sustained behavior change [73].

Aim and outline of this thesis

The aim of this thesis is to optimize HIV/STI care in MSM by exploring the barriers to current HIV/STI care and possible solutions in order to optimize the number of MSM that will be reached and provide them with optimal recommended test and care. In this thesis I will look into two components of infection transmission control, decreasing probability of transmission per contact and decreasing the duration of infectiousness.

Decrease probability of transmission per contact: hidden reservoirs

In the first section we assess the probability of transmission by exploring a possible transmission route and hidden reservoirs for unexplained anorectal infections. In **chapter 2** we assess the role of an oropharyngeal infection on anorectal infection and study the relation between previous CT infection and subsequent anorectal infection in MSM and women visiting STI clinics in the Netherlands. In addition, in **chapter 3** we advise to take caution in drawing conclusion on the 'oropharyngeal-anorectal chlamydia hypothesis'.

Decrease duration of infectiousness: testing and treatment

In the second section we explore options to decrease the duration of infectiousness by exploring the needs and barriers among MSM for HIV/STI testing. **Chapter 4** provides insight in HIV testing behaviour of MSM living in different geographic areas in the Netherlands. **Chapter 5** describes the systematic development of a home-care program with self-sampling for HIV and sexually transmitted infections for MSM. In **chapter 6** we evaluate the pilot implementation of this home-care program in HIV-positive MSM.

In **chapter 7** the main findings of this thesis are discussed and recommendations for optimizing HIV/STI care in MSM and suggestions for future research are provided.

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Probability of transmission

Role of oral chlamydia trachomatis in anorectal CT positivity

CHAPTER 2

A longitudinal study to investigate previous infection as a risk factor for subsequent anorectal infection in men who have sex with men (MSM) and women visiting STI clinics in the Netherlands

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Abstract

Although anorectal Chlamydia trachomatis (CT) infections are frequently diagnosed in men who have sex with men (MSM) and women, the reason for this infection often remains unexplained, as anal sex is not always reported. Oropharyngeal infections inoculating the gastrointestinal (GI) tract may contribute to anorectal-CT infections, as evidence in animals suggests that chlamydia bacteria undergo GI passage; however, no evidence exists in humans.

Longitudinal patient clinic-registry data from MSM (n = 17 125) and women (n = 4120) from two Dutch sexually transmitted infection clinics were analysed.

When adjusting for confounding socio-demographics, co-infections and risk behaviour, previous (from 3 weeks up to 24 months) oropharyngeal CT was not a risk factor for subsequent anorectal CT in women(odds ratio (OR) 0.46; 95% confidence interval (CI) 0.18–1.18; P = 0.11) and MSM (OR 1.33; 95% CI 0.86–2.07; P = 0.204).

Despite the large dataset, the numbers did not allow for the estimation of risk in specific subgroups of interest. The role of the GI tract cannot be excluded with this epidemiological study, but the impact of preceding oropharyngeal CT on anorectal-CT infection is likely limited.

Background

Anorectal infections with Chlamydia trachomatis (CT) are commonly found in men who have sex with men (MSM) and in women. The prevalence is reported to be between 1% and 18% for MSM and between 6% and 17% for women [1–5]. Anorectal-CT infections are often asymptomatic (36–100%) [1, 6, 7] and are frequently (~50–65%) detected in MSM and women who did not report anal sex [6, 8, 9]. In women, self-infection (autoinoculation) from the genital site is postulated as an explanation for the detection of anorectal CT in the absence of anal sex, as most anorectal infections co-occur with genital-CT infections in women [10]. Another theory to explain anorectal-CT infections in women and MSM involves the oropharyngeal site and the gastrointestinal (GI) tract serving as a reservoir for CT [11–13]. There is an on-going debate on whether humans can host CT bacteria in the intestine and develop an anorectal infection via contamination from the lower GI tract, as described in several animal studies [11, 12, 14].

Chlamydia species are commensal bacteria in the gut of many animals, such as mice, birds, sheep and cattle [11]. Chlamydia bacteria have been proven to be able to survive in the GI tract of animals for a long time (up to 3 years) without causing an immune reaction through down-regulation of the immune system in the gut, as no inflammatory response was seen in histopathological examination of chlamydia-infected tissue [11, 15, 16]. In a study by Yeruva et al., mice were orally infected with *Chlamydia muridarum*; after 10 days, the bacteria could be detected in the caecum and large intestine. Chlamydia might survive the acidic environment of the stomach and remain in the lower intestinal tract [12]. Studies have shown that animals with chlamydia bacteria in the GI tract continue to shed organisms for a long period of time, even up to 4 years [12, 16]. Chlamydia bacteria seem to be able to pass through the GI tract to the anorectal area, at least in animals. Although some evidence for an oropharyngeal–anorectal route exists in animals, no conclusive relationship between oropharyngeal CT (or lymphogranuloma venereum (LGV)) and the GI tract in humans has been demonstrated yet.

The only evidence in humans includes studies with infants born to CT-infected mothers. Those studies conclude that, persistent GI chlamydial infection might also occur in humans [14, 17]. In a study by Schachter et al., some of the infants born to CT-infected mothers became CT-colonised in the anorectal region after 41–79 days of age. This later onset raised questions regarding if CT colonisation in the GI tract was possible in these infants [14].

Nevertheless, it is debatable whether positive anorectal cultures are the result of chlamydia bacteria in the intestine. Infants could also become CT-infected via the respiratory tract, rectum or vagina through perinatal exposure [14].

Bavoil et al. hypothesised that active oral sex (fellatio) could lead to the colonisation of the GI tract with infectious chlamydia bacteria and, from there, contaminate and infect the rectum and female genital tract [13]. For LGV, a specific CT type that mainly occurs in MSM, it was carefully suggested that oropharyngeal infections might play a role in inducing anorectal LGV via the GI tract, thereby potentially contributing to its on-going transmission [18]. However, the relationship between oropharyngeal and anorectal-CT infection in humans has not yet been studied extensively, because human experiments are hampered for medical ethical reasons, and therefore, whether such association exists remains unclear.

Another approach to study this is through the use of retrospective clinical data of patients who visited a sexually transmitted infection (STI) clinic multiple times. In the current study, we analysed the association between preceding oropharyngeal and subsequent anorectal CT in MSM and women using a large set of retrospective patient clinic-registry data from two STI clinics.

Methods

The outpatient STI clinics of the Public Health Services in Amsterdam and South Limburg offer free STI testing to at-risk groups with and without symptoms, including those attending after partner notification. Women and MSM aged 16 years and older, who visited the STI clinic from January 2006 to December 2013, were included (see figure 1).

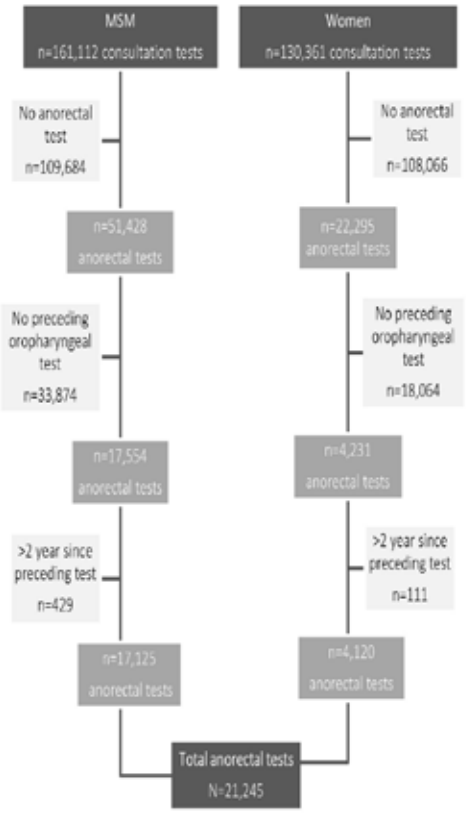

Figure 1. Flow chart of study population between January 2006 and December 2013 (testing consultations).

Because the retrospective coded data originated from standard care and were analysed anonymously, neither a full ethical review nor informed consent for data analysis was needed, as confirmed and approved by the Medical Ethical Committee of Maastricht University (METC 11-4-108).

Study procedures: testing

Patients were routinely tested for urogenital CT and Neisseria gonorrhoeae (NG). MSM were tested for anorectal and oropharyngeal CT when indicated (i.e. after the self-report of anal sex or symptoms). From 2010 onwards, MSM were routinely tested for anorectal and oropharyngeal CT in South Limburg. In Amsterdam, MSM were routinely tested for oropharyngeal CT since 2011. Women who were notified, reported symptoms or were paid for sex were tested for anorectal and oropharyngeal CT (since 2011, Amsterdam) [19].

Specimens tested for CT consisted of urine (MSM), self-collected vaginal and/or anorectal swabs, nurse-collected oropharyngeal swabs and clinician-collected cervical and urethral swabs. Tests were performed according to the manufacturer's protocol. In South Limburg, specimens were processed at two regional laboratories using three different nucleic acid amplification assays (SDA, Becton Dickinson ProbeTec ET system, Maryland, USA, until 2012; Cobas Amplicor, Roche, California, USA, 2006–2011; Cobas 4800, Roche, California, USA, since 2012). In Amsterdam, from 2008 the Aptima Combo 2 Assay for CT/NG has been used to detect rRNA (Hologic Gen-Probe Inc., San Diego, USA). Before 2008, the Cobas Amplicor was used. Culture was also used in case of symptoms, being notified for STI, paid for sex or MSM for oropharyngeal (until 2008), urogenital and anorectal NG. Each consultation included a standardised nurse-collected medical and sexual history [19].

Statistical analyses

Dataset

Two subsequent visits from one person were taken as a measurement pair, based on an anonymised person identifier. Between the first (preceding) and second (subsequent) visit (measurement pair), there was a time-window ranging from 21 days up to 730 days. This timeframe was chosen because the bacteria may need time to reach the GI tract, and it has been found that animals with chlamydia bacteria in their gut continued to shed chlamydia organisms for several years [12, 16].

A person could be included in the dataset with multiple measurement pairs (or so-called repeated measurements) when he or she visited the STI clinic more than two times between 2006 and 2013. Measurement pairs were included in analyses when the preceding visit had (at least) an oropharyngeal-CT test, and the subsequent visit had (at least) an anorectal-CT test.

Missing values were treated as a separate category, except for where the number of missing values was small (<25). In such case missing values were attributed to the most likely value, i.e. cases that had missing results for preceding urogenital CT (n = 6), subsequent urogenital CT (n = 10), urogenital NG (n = 21) and anorectal NG (n = 18) were defined as negative.

Generalised Estimating Equation (GEE)

Univariate and multivariate GEE analyses were used to estimate the association between preceding (⩽24 months) oropharyngeal CT and subsequent anorectal CT. GEE analysis took into account the repeated measurements and therefore corrected for individuals bringing more measurement pairs into the data than others.

All analyses were stratified for MSM and women because of the different testing guidelines for both groups [1]. For MSM, all univariate confounders were statistically significant ($P < 0.05$) and thus added to the multivariate model. For women, a multivariable model was constructed by adding variables in groups (socio-demographic, co-infections and risk behaviour) to the model using a stepwise backward approach, and thus not included variables that were not statistically significant in univariate analyses.

Main effect

To assess the association between preceding oropharyngeal and subsequent anorectal CT, oropharyngeal CT at the preceding consultation was defined as the main exposure variable of interest. A priori, as epidemiological associations may be subject to confounding, the main effect was adjusted for several confounding factors. Correction was deemed essential, especially in studying this association, as oropharyngeal-CT infection may also represent high risk sexual behaviour, which is also highly associated with anorectal CT [1, 4].

Confounders

General socio-demographic confounders included in the model were age (<30, 30–45, >45 years) and STI clinic (Amsterdam, South Limburg).

Co-infections with oropharyngeal CT, urogenital CT, urogenital NG, anorectal NG, HIV (MSM) and syphilis, as well as preceding anorectal- and urogenital-CT and -NG infections were considered important surrogate markers for risk behaviour (i.e. unsafe sex) and considered as potential confounders.

Other proxies for risk behaviour included being notified for STI, new sex partners in the past 6 months (data only available from the STI clinic in Amsterdam), number of sex partners in

the past 6 months and self-reported receptive anal sex in the past 6 months. Genital and anorectal symptoms were testing indications and therefore included in the model. In MSM, receptive anal sex is defined as such when (1) MSM were tested anorectally before 2012 at the STI clinic South Limburg and Amsterdam, (2) receptive anal sex was reported at the STI clinic in Amsterdam since 2012 or (3) anal sex was reported at the STI clinic in South Limburg for the whole study period. Guidelines advised to treat chlamydia infections with a single dose azithromycin 1000 mg [20]. From 2012, national guidelines advised to treat anorectal chlamydia infections with doxycycline 100 mg two times per day for 7 days [21]. In Amsterdam, patients were treated with doxycycline for anorectal chlamydia infections during the whole study period (personal communication).
We considered a P-value of <0.05 as statistically significant in univariate and multivariate analyses. All analyses were performed using SPSS version 20.0 (IBM Inc., Somers, NY, USA).

Sensitivity analyses

Since testing guidelines changed after 2010, additional analyses were performed by restricting data to tests from 2010 onwards. Other sensitivity analyses were performed by comparing women who reported anal sex with those who did not report anal sex. Due to low subgroup numbers (n = 5), risk factor analyses for MSM who did not report anal sex or for patients who had a single-anorectal infection was not possible due to the low numbers of preceding oropharyngeal infections in the included measurement pairs of these sensitivity analyses (Table 1).

Table 1. Subgroups with oropharyngeal CT infection on the preceding visit.

	N	Subsequent anorectal positivity n (%)
Timeframe		
MSM		
<6 months	139	17 (12.2%)
<12 months	191	25 (13.1%)
Women		
<6 months	60	8 (13.3%)
<12 months	74	8 (10.8%)
Concurrent urogenital CT		
MSM		
Positive	1	1 (100%)
Negative	7	4 (57.1%)
Not tested	200	25 (12.5%)
Women		
Positive	10	9 (90%)
Negative	70	0 (0%)

Descriptive sensitivity analyses included restrictions to shorter time intervals between measurement pairs (≤12 months and ≤6 months) and with patients who had a single-anorectal CT (without concurrent urogenital CT). This was done to obtain insight into the effect of concurrent urogenital infections (see Table 1).

Results

Characteristics

The analyses included 21,245 measurement pairs consisting of a preceding clinic visit with (at least) an oropharyngeal-CT test and a subsequent clinic visit with an anorectal-CT test. MSM contributed 17,125 (80.6%) measurement pairs, and women contributed 4,120 (19.4%) measurement pairs. Every individual had at least one measurement pair, with a MAXIMUM of 24 pairs. The data included 7,272 unique individuals: 5.493 MSM (75.5%) and 1,779 women (24.5%). For MSM, the median age was 40 (range: 16–79, interquartile range (IQR): 33–47) in Amsterdam and 43 (range: 16–74, IQR: 32–50) in South Limburg (P < 0.001). For women, the median age was 27 (range: 17–66, IQR: 23–34) in Amsterdam and 44 (range: 18–63, IQR: 38–49) in South Limburg. At the first (preceding) visit of the measurement pairs, oropharyngeal-CT positivity was 1.2% for MSM (n = 208) and 1.9% for women (n = 80). At the subse-

quent visit of the measurement pairs, anorectal-CT positivity was 7.7% for MSM (n = 1,316) and 5.4% for women (n = 224).

Main effect unadjusted

In univariate analyses, preceding oropharyngeal CT was associated with subsequent anorectal CT in MSM (odds ratio (OR) 2.05, 95% confidence interval (CI) 1.40–3.01, P < 0.0001) and in women (OR 2.26, 95% CI 1.06–4.80, P = 0.04) (Tables 2 and 3).

Table 2. Absolute numbers and prevalences of anorectal Chlamydia trachomatis infections and univariate and multivariate risk factors using generalised estimating equation analyses in MSM.

	Characteristics		Anorectal positive		Univariate [1]	Multivariate [1,2]
Main effect	n	(%)	n	(%)	odds ratio (95%CI)	odds ratio (95%CI)
Previous oropharyngeal CT						
Positive	208	1.2	30	14.4	**2.05 (1.40, 3.01) *****	1.33 (0.86, 2.07)
Negative	16,917	98.8	1,286	7.6	1	1
Confounding						
Socio-demographic						
Age (years)						
<30	2,970	17.3	261	8.8	**1.46 (1.21, 1,76) *****	**1.52 (1.25, 1.85) *****
30-45	8,409	49.1	699	8.3	**1.37 (1.18, 1.60) *****	**1.31 (1.13, 1.52) *****
>45	5,746	33.6	356	6.2	1	1
STI clinic location						
Amsterdam	13,241	77.3	1,108	8.4	**1.61 (1.33, 1.95) *****	1.26 (0.94, 1.69)
Limburg	3,884	22.7	208	5.4	1	1
Co-infections						
Current oropharyngeal CT						
Not tested	68	0.4	6	8.8	1.25 (0.54, 2.90)	1.48 (0.57, 3.84)
Positive	187	1.1	99	52.9	14.56 (10.76, 19.70) ***	11.82 (8.26, 16.89) ***
Negative	16,870	98.5	1,211	7.2	1	1
Current urogenital CT						
Not tested	59	0.3	5	8.5	1.29 (0.52, 3.24)	1.16 (0.43, 3.13)
Positive	586	3.4	210	35.8	**7.81 (6.49, 9.39) *****	**6.12 (4.94, 7.57) *****
Negative	16,480	96.2	1101	6.7	1	1
Previous urogenital CT						
Not tested	56	0.3	5	8.9	1.20 (0.48, 3.03)	1.11 (0.40, 3.10)
Positive	637	3.7	71	11.1	**1.52 (1.17, 1.95) ****	0.90 (0.67, 1.20)
Negative	16,432	96.0	1,240	7.5	1	1
Previous anorectal CT						
Not tested	1,082	6.3	81	7.5	1.07 (0.84, 1.36)	1.28 (0.98, 1.66)

Positive	1,422	8.3	207	14.6	**2.25 (1.89, 2.67) *****	**1.53 (1.26, 1.86) *****
Negative	14,621	85.4	1,028	7.0	1	1
Current genital NG						
Not tested	43	0.3	2	4.7	0.60 (0.15, 2.42)	0.70 (0.15, 3.13)
Positive	361	2.1	57	15.8	**2.31 (1.75, 3.05) *****	0.77 (0.54, 1.08)
Negative	16,721	97.6	1,257	7.5	1	1
Current anorectal NG						
Not tested	48	0.3	4	8.3	1.26 (0.45, 3.52)	1.01 (0.32, 3.15)
Positive	877	5.1	218	24.9	**4.58 (3.85, 5.44) *****	**2.91 (2.39, 3.56) *****
Negative	16,200	94.6	1,094	6.8	1	1
Current HIV						
Not tested	48	0.3	6	12.5	**2.54 (1.17, 5.56) ***	1.88 (0.77, 4.61)
Positive	6,072	35.5	725	11.9	**2.41 (2.13, 2.74) *****	**2.06 (1.79, 2.38) *****
Negative	11,005	64.3	585	5.6	1	1
Current Syphilis						
Not tested	1,531	8.9	95	6.2	0.80 (0.62, 1.03)	1.25 (0.91, 1.71)
Positive	387	2.3	58	15.0	**2.13 (1.60, 2.84) *****	1.26 (0.92, 1.74)
Negative	15,207	88.8	1,163	7.6	1	1
Risk behaviour						
Receptive anal sex						
Unknown	2,637	15.4	175	6.6	**4.07 (2.81, 5.88) *****	**3.16 (2.16, 4.61) *****
Yes	12,388	72.4	1,104	8.9	**5.60 (4.00, 7.84) *****	**2.73 (1.91, 3.90) *****
No	2,096	12.2	36	1.7	1	1
Self-reported symptoms						
Yes	3,787	22.1	495	13.1	**2.29 (2.02, 2.59) *****	**1.43 (1.25, 1.64) *****
No	13,338	77.9	821	6.2	1	1
Being notified for STI						
Yes	2,531	14.8	370	14.6	**2.48 (2.17, 2.83) *****	**1.76 (1.52, 2.04) *****
No	14,594	85.2	946	6.5	1	1
New sex partner						
Yes	13,773	80.4	1,143	8.3	**1.66 (1.40, 1.97) *****	1.02 (0.78, 1.33)
No	3,352	19.6	173	5.2	1	1
Number of sex partners in the past 6 months						
Unknown	170	1.0	14	8.2	1.62 (0.93, 2.83)	1.41 (0.72, 2.75)
>3	12,128	70.8	1,049	8.6	**1.71 (1.48, 1.98) *****	**1.40 (1.12, 1.75) ****
≤3	4,827	28.2	253	5.2	1	1

CT *Chlamydia trachomatis*; NG *Neisseria gonorrhoeae*; STI Sexually transmitted infection; MSM Men who have sex with men; CI Confidence interval.

[1] Confidence intervals that do not overlap the null value of odds ratio=1 are shown in bold.

[2] Controlled for sociodemographic factors and proxies for risk behaviour.

*p<0.05

**p<0.01

***p<0.001

Table 3. Absolute numbers and prevalences of anorectal Chlamydia trachomatis infections and univariate and multivariate risk factors using generalised estimating equation analyses in women.

	Characteristics		Anorectal positive		Univariate[1]	Multivariate [1,2]
Main effect	n	(%)	n	(%)	odds ratio (95%CI)	odds ratio (95%CI)
Previous oropharyngeal CT						
Positive	80	1.9	9	11.3	**2.26 (1.06, 4.80)** *	0.46 (0.18, 1.18)
Negative	4,040	98.1	215	5.3	1	1
Confounding						
Socio-demographic						
Age (years)						
<30	1,566	38.0	122	7.8	**2.43 (1.54, 3.83)** ***	**2.01 (1.11, 3.62)** *
30-45	1,633	39.6	71	4.3	1.31 (0.80, 2.13)	1.52 (0.82, 2.79)
>45	921	22.4	31	3.4	1	
STI clinic location[3]						
Amsterdam	2,321	56.3	149	6.4	**1.58 (1.15, 2.16)** **	
Limburg	1,799	43.7	75	4.2	1	
Co-infections						
Current oropharyngeal CT						
Not tested	386	9.4	40	10.4	**2.65 (1.83, 3.84)** ***	1.64 (0.96, 2.80)
Positive	47	1.1	30	63.8	**40.49 (22.47, 72.96)** ***	**13.28 (4.67, 37.73)** ***
Negative	3,687	89.5	154	4.2	1	
Current urogenital CT						
Positive	237	5.8	157	66.2	**111.78 (76.51, 163.28)** ***	**95.26 (63.05, 143.95)** ***
Negative	3,883	94.0	67	1.7	1	1
Previous urogenital CT[3]						
Positive	302	7.3	41	13.6	**3.12 (2.15, 4.52)** ***	
Negative	3,818	92.7	183	4.8	1	
Previous anorectal CT						
Not tested	1,151	27.9	84	7.3	**1.80 (1.35, 2.39)** ***	1.78 (1.17, 2.69) **
Positive	182	4.4	23	12.6	**3.30 (1.99, 5.47)** ***	3.00 (1.36, 6.59) **
Negative	2,787	67.6	117	4.2	1	
Current genital NG [3]						
Positive	59	1.4	12	20.3	**4.64 (2.44, 8.82)** ***	
Negative	4,061	98.6	212	5.2	1	
Current anorectal NG [3]						
Positive	48	1.2	11	22.9	**5.39 (2.74, 10.59)** ***	
Negative	4,072	98.8	213	5.2	1	
Risk behaviour						
Receptive anal s ex[3]						
Unknown	681	16.5	26	3.8	0.92 (0.57, 1.48)	
Yes	1,731	42.0	127	7.3	**1.83 (1.35, 2.47)** ***	

No	1,708	41.5	71	4.2	1	
Self-reported symptoms[3]						
Yes	633	15.4	52	8.2	**1.73 (1.24, 2.41)** **	
No	3,487	84.6	172	4.9	1	
Being notified for STI						
Yes	272	6.6	39	14.3	**3.31 (2.26, 4.87)** ***	1.97 (1.07, 3.63) *
No	3,848	93.4	185	4.8	1	1
New sex partner[3]						
Yes	3,586	87.0	179	5.0	**0.57 (0.41, 0.80)** **	
No	534	13.0	45	8.4	1	
Number of sex partners in the past 6 months[3]						
Unknown	113	2.7	6	5.3	0.61 (0.26, 1.43)	
>3	692	16.8	58	8.4	**0.55 (0.40, 0.76)** ***	
≤3	3,315	80.5	160	4.8	1	

CT *Chlamydia trachomatis*; NG *Neisseria gonorrhoeae*; STI Sexually transmitted infection; MSM Men who have sex with men; CI Confidence interval.
[1] Confidence intervals that do not overlap the null value of odds ratio=1 are shown in bold.
[2] Controlled for sociodemographic factors and proxies for risk behaviour.
[3] Not included in final model by back step procedure.
*p<0.05
**p<0.01
***p<0.001

Main effect adjusted for confounders

For MSM, the addition of socio-demographic confounders to the model decreased the OR from 2.05 (95% CI 1.40–3.01, P < 0.0001) to 1.97 (95% CI 1.33–2.91, P = 0.001). By adding co-infections, the OR decreased further to 1.35 (95% CI 0.87–2.10, P = 0.180), and, by adding proxies for risk behaviour, the OR decreased to 1.33 (95% CI 0.86–2.07, P = 0.204).
For women, the addition of socio-demographic confounders to the model decreased the OR from 2.26 (95% CI 1.06–4.80, P = 0.04) to 1.98 (95% CI 0.93–4.21, P = 0.08). Adding co-infections further decreased the OR to 0.48 (95% CI 0.19–1.20, P = 0.12) and by adding proxies for risk behaviour to OR 0.46 (95% CI 0.18–1.18, P = 0.11).

Confounders in the model and their association with anorectal CT

Associated factors for the subsequent anorectal CT in MSM were concurrent oropharyngeal CT, urogenital CT, anorectal NG, HIV, preceding anorectal CT, younger age (<34 years and between 30 and 45 years), self-reported anal sex, report of genital or anal symptoms and notification of an STI (Table 2). For women, risk factors for anorectal CT were younger age (<34 years), concurrent oropharyngeal CT, urogenital CT, preceding anorectal-CT infection and notification of an STI (Table 3).

Sensitivity analyses for the main effect

When restricting to a shorter time interval, the OR for MSM was 1.21 (95% CI 0.77–1.92, P = 0.41) for ≤12 months between preceding and subsequent visit and 1.15 (95% CI 0.68–1.93, P = 0.61) for ≤6 months. For women, the adjusted OR was 0.54 (95% CI 0.21–1.39, P = 0.20) for ≤12 months and the adjusted OR was 0.73 (95% CI 0.29–1.86, P = 0.51) for ≤6 months.
Of the women who had a preceding oropharyngeal-CT infection, none had subsequent anorectal-only CT infection (without concurrent urogenital CT), and nine had both anorectal- and urogenital-CT infection (see Table 1).
When restricting data from 2010 onwards, the adjusted OR for MSM was 1.21 (95% CI 0.76–1.91, P = 0.42). For women, the adjusted OR was 0.44 (95% CI 0.16–1.17, P = 0.10).
The adjusted OR for women who did not reported anal sex was 0.37 (95% CI 0.08–1.7, P = 0.20) and for women who reported anal sex the OR was 0.39 (95% CI 0.09–1.66, P = 0.20).

Discussion

Preceding oropharyngeal-CT infection is not an independent risk factor for subsequent anorectal-CT infection in MSM and women, using epidemiological methods.

Because a causal relationship between oropharyngeal and anorectal CT cannot be studied through human experiments due to medical ethical restrictions, epidemiological assessment using a retrospective longitudinal design is the next best approach. In this study, using patient clinic-registry data, a large number of MSM and women (n = 7,272) screened for oropharyngeal CT were included in analyses. To the best of our knowledge, this is the first large human study assessing oropharyngeal CT as a predictor of subsequent anorectal CT using longitudinal data. It has been shown that many factors are epidemiologically associated with anorectal CT [22–24]. Therefore, the availability of a broad range of both sociodemographic factors and risk behaviour factors enabled adjustments for confounding factors, and the adjustment for these in analyses is a major asset of this study.
GEE analysis was considered to be the most suitable analysis for this study with repeated measurements. Analysis of variance and multivariate analysis of variance are other types of analyses for repeated measurements; however, these analyses are not able to incorporate covariates. Logistic regression analyses do not take repeated measurements into account, and survival analyses do not take into account repeated measurements from the same individual.

However, this retrospective cohort study is not without limitations. First, due to our clinics' testing policy (as in international guidelines [1]), only a select group of high-risk patients (patients who were notified, reported symptoms or commercial sex workers) were oropharyngeally tested. This could lead to an overestimation of the prevalence of oropharyngeal CT and an underestimation of the absolute number of oropharyngeal infections; however, the direction of possible bias in the risk estimates is unknown. Also, testing guidelines changed during the study period, which could lead to sampling bias of our dataset. This may influence the generalisability of our sample; it should not affect the biological association of previous oropharyngeal and subsequent anorectal CT. When restricting data to include only data collected during the latest guidelines (from 2010 onwards), sensitivity analyses showed similar results as when including data from all years.

Second, exposure may be misclassified when there were oropharyngeal infections that occurred after a clinic visit or spontaneously resolved before the visit [25], as these would be missed as exposures in the analyses. This may lead to an underestimation of the risk of anorectal CT. However, such bias may be considered limited, especially because oropharyngeal-CT infections have been found to have a low bacterial load [25] and therefore may not survive the GI tract. On the other hand, multiple low load oropharyngeal infections could accumulate in the GI tract and result in a rectal infection. However, there is no scientific evidence for survival and accumulation of CT in the human GI tract. In subcategories with missing values, where the number of cases was small, missing values were attributed to the most likely value. Although it is possible that these missing values were wrongly attributed, the numbers were small and thereby unlikely to affect the main effect.

Third, in spite of correction of confounders, we could not completely rule out residual confounding, such as confounding due to the lack of information on several variables. Because our study used routinely collected data originated from standard care, there was no information available on condom use, bacterial load, whether patients swallowed ejaculate, genotyping and the given treatment regime. Because genotyping was not available, we could not identify whether anorectal-CT infections originated from the same bacteria as the preceding oropharyngeal infections. In our study design, we hypothesise that the oropharyngeal and anorectal infection are of the same genotype. Therefore, the effect of the oropharyngeal–anorectal CT hypothesis could be overestimated, as in real life genotypes could be different. Yeruva et al. showed in mice that although azithromycin is able to clear the genital tract, but is unable to eliminate chlamydial infection in the GI tract with the same dose within the same animal [26]. This suggests that the GI tract may have a differential susceptibility of chlamydiae to azithromycin than the genital tract and thus could possibly

reflect failure of antibiotic treatment for the GI tract. We could not assess the effect of this phenomenon on our study results, as the exact treatment regime received by patients was not recorded in the routinely collected data originating from standard care used in this study.

Fourth, although this study included a large number of measurement pairs, these numbers did not allow for the estimation of risks in specific subgroups of interest (such as MSM with a preceding oropharyngeal infection who did not report anal sex). For example, in women, genital infection may lead to anorectal positivity by autoinoculation, which can have an impact on the number of anorectal infections, thereby influencing the relationship found between oropharyngeal and anorectal infections [4, 10, 23, 27]. Although we corrected for urogenital-CT infections in the model, the number of women with anorectal-only CT infections (and in whom the role of autoinoculation could be excluded) was too low for a risk factor analysis.

Fifth, if there was an association between the oropharyngeal and subsequent anorectal-CT infections, it could reflect a higher risk of oropharyngeal CT due to risk behaviour, instead of a true association between the two types of CT infections. However, adjusting for confounding factors could have led to an overcorrection and underestimation of the main effect. Nevertheless, correction was deemed necessary, provided unique insight into the relationship between oropharyngeal and anorectal-CT infections, and corrected for high-risk behaviours for STI.

Previous studies presented results in favour of the hypothesis that oropharyngeal CT could lead to anorectal CT via the GI tract [11, 12, 15, 18, 28]. Bavoil et al. hypothesised that oral sex could introduce CT to the GI tract, which then could infect the rectum [13]. However, most of these studies based their findings mainly on animal studies. To our knowledge, there are no epidemiological studies that look at preceding oropharyngeal and subsequent anorectal-CT infections in humans. More studies with human data are needed, with, for example, data on the routine testing of all anatomic sites and genotyping in order to compare our study findings on the oropharyngeal–anorectal CT hypothesis.

Despite these limitations, we showed robustness of our results by doing several sensitivity analyses and taking into account some of the abovementioned limitations.

Overall, it is possible that anorectal-CT infections caused by oropharyngeal-CT infections might not have surfaced in this study. However, if no such association was found in this large-scale retrospective data that included high-risk STI clinic visitors, it is unlikely that there will be an association in the general population. The external validity of this study is low, because individuals tested multiple times at the STI clinic belong to a group at high-risk

for STI. Potential associations that were missed, for example, due to spontaneous clearance and the low prevalence of oropharyngeal-CT infections, would have been small and had a limited impact on public health; in other words, it would have a minor impact on transmission at the population level and on STI care in practice.
In conclusion, this large longitudinal study did not discover any risk from preceding oropharyngeal CT for subsequent anorectal-CT infection. A possible minor association with a potential impact on a limited number of individual patients cannot be ruled out, as we used an epidemiological design rather than human experiments, but the impact of such possible association on public health is likely to be small.

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CHAPTER 3

Proceed with caution in generating evidence in the 'oropharyngeal-anorectal chlamydia hypothesis' in humans

Authors:

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Sexually transmitted diseases (2019)

To the editor – There is an on-going debate on whether oropharyngeal Chlamydia trachomatis (CT) infections can inoculate the human gastrointestinal tract, and subsequently lead to anorectal CT infections [1-3]. Evidence in animals suggests that chlamydia bacteria can undergo gastrointestinal passage [1, 2]. However, no evidence exists in humans. We have read the article by Batteiger et al. with great interest and compliment the authors with their attempt to provide answers on this hypothesis in humans [4]. The authors assume that oral sex (cunnilingus) leads to oropharyngeal CT infections, as they look into the relation between oral sex and anorectal infections, without testing for oropharyngeal CT infection. Although there have been speculations [3], it has not yet been proven that oral sex leads to oropharyngeal CT infections. The authors conclude that anorectal CT infections could result from inoculation via the GI tract after the self-report of oral sex. From an epidemiological point-of-view, the current study does not provide enough evidence to draw this conclusion [5].

Batteiger et al. used a cross-sectional study design. This design is often chosen to report descriptives or prevalence and lacks the ability to infer causality [6]. In their study, no statistical tests or adjustment for potential confounders were done to assess the relation between cunnilingus and anorectal CT. Additionally, the authors did not describe a control group. Among men who did not report cunnilingus or reported anal behaviors, none had anorectal CT (0%; 95% confidence interval [CI], 0.0-0.7). When we look at men who report cunnilingus and denied anal sex behaviors, 2 (2.4%) men had anorectal CT infection (95% CI, 0.3-8.3). The confidence intervals of both groups are large and overlap. The exact difference between these groups (2.4%; 95%CI, -0.88-5.64) includes zero, and thus there is no difference between both groups. Moreover, the power of the study is low, as the authors based their findings on a population of 84 men, of which 2 were anorectally CT positive. Because of these small sample numbers this finding could be based on coincidence. The 2 anorectal CT infections could be acquired through other ways (e.g. underreported anorectal behavior). We compliment the authors in their efforts to maximize the accuracy of the self-reported sexual behaviors. However, as the authors describe in their discussion, when using self-reported data it can not be ruled out that these self-identified heterosexual men had engaged in anorectal activities and thus information bias could have occurred [7]. This is not unlikely as they showed that men who identify themselves as heterosexual also report anorectal sex or sex with men.

We studied the oropharyngeal-anorectal hypotheses using a large longitudinal dataset of MSM and women (n=21,245) and found no statistically significant independent association between preceding oropharyngeal and subsequent anorectal infections (adjusting for confounders) [8]. Although cross-sectional studies do not have the optimal design to infer causality, Batteigers' study contributes to understanding the oropharyngeal-anorectal hypothesis in humans. However, in our view, the scientific evidence from Batteigers et al. is too weak to draw conclusions regarding the oropharyngeal-anorectal hypothesis in humans and we advise caution for overinterpreting results.

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2

Duration of infectiousness

HIV/STI Testingy

CHAPTER 4

HIV testing behavior and associated factors in men who have sex with men by level of urbanization: A cross-sectional study in the Netherlands

Authors:

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Abstract

Regular HIV testing in men who have sex with men (MSM) enables timely entry into care and reduces the likelihood of HIV transmission. We aimed to assess HIV-testing behavior and associated factors in MSM by urbanization of place of residence.

Data were derived from online survey ('Men & Sexuality') in the Netherlands. HIV testing was defined as recent (<1 year), not recent (≥1 year), or never. Using multinominal regression analyses, factors associated with not recent testing and never testing, compared to recent testing, were assessed among 3,815 MSM living in highly (>2,500 residences/km2) or non-highly (≤2,500 residences/km2) urbanized areas.

In highly urbanized areas, 11.8% was never and 19.8% was not recently HIV-tested. In non-highly urbanized areas, this was 25.2% and 19.6%. Among MSM living in highly urbanized areas, independently associated with never and not recent testing were younger age, self-identification as bisexual, fewer sex partners, never notified of HIV, and no recent condomless anal intercourse. Among MSM living in non-highly urbanized areas, lower perceived HIV severity, higher perceived HIV risk, and a lower proportion gay friends, were associated with never and not recent testing. Among never tested MSM, those in non-highly urbanized areas preferred self-sampling/self-testing over facility-based testing, those in highly urbanized areas preferred testing at healthcare facilities.

The proportion of never tested MSM was high (25%) in non-highly urbanized areas in the Netherlands. MSM living in non-highly urbanized areas may possibly be reached with targeted approaches to increase HIV testing uptake such as self-testing/self-sampling strategies.

Background

Men who have sex with men (MSM) have been disproportionately affected by the HIV epidemic. In Europe, most countries prioritize MSM as a key population in their HIV response. In the Netherlands, more than 20 000 people are living with HIV, with 482 new HIV diagnoses in the year 2019, of which the majority (64%) were MSM [1]. Regular HIV testing of people at risk for HIV enables early initiation of antiretroviral drug treatment (ART), and is associated with virologic, immunological, and clinical benefits [2]. People with later stage HIV infections have a higher risk of progressing to AIDS or death, and have higher direct medical treatment expenditures [3].

Universal and frequent HIV testing, in combination with timely treatment, has the potential to eliminate HIV [4]. Further efforts to expand testing services and increase accessibility and availability to key populations must be undertaken to reduce the number of people who are living with undiagnosed HIV or in whom HIV is diagnosed late.

In the Netherlands, options for HIV testing are widespread and available, and sexual health facilities are in place. However, an estimated 15%–20% of all MSM living with HIV were undiagnosed in 2010–2015 [5, 6]. In 2018, an estimated 1,000 MSM (800–1,300) with HIV were still undiagnosed and an estimated 92% of people living with HIV have been diagnosed and linked to care in the Netherlands [1]. Among MSM who attend Dutch sexually transmitted infection (STI) clinics, a minority (19%) tests regularly, that is, 6-monthly, as suggested by the national testing guidelines. Other testing facilities include the general practitioner (GP) and self-testing options. In the Netherlands, Australia, and the UK, the estimated overall proportion of MSM testing at least once per year ranged between 33% and 36% [7].

A range of factors have previously been found to be associated with HIV testing; of the socioeconomic factors, urbanization level is a well-known factor [8]. Differences in health between people living in low and highly urbanized areas represent worldwide challenges. The proportion of MSM who had not (recently) tested or MSM who were diagnosed at a later stage and entered care at later stages of infection was found to be higher in less urbanized areas [8-10]. People living in low urbanized areas may face geographical barriers and may have lower access to health information sources [11, 12].

Knowledge on HIV testing and associated factors in MSM by levels of urbanization can be used to enhance the HIV-testing strategies tailored to the urbanization-setting. Therefore, this study aimed to assess the factors associated with the never tested and not recently tested MSM living in different urbanized areas in the Netherlands, using an internet survey.

Methods

Between February and June 2018, the online survey 'Men & Sexuality' (SMS) was conducted in the Netherlands and is reported elsewhere in greater detail [13]. In short, the cross-sectional survey was designed to assess health, well-being, and sexuality among MSM. Inclusion criteria were being male, aged 16 years or older, currently living in the Netherlands, and one of the following: (1) ever had sex with men, (2) attracted to men, or (3) expected to have sex with men in the future. This online survey reached MSM from all over the Netherlands, as it was mainly advertised on social media (Facebook and Instagram), dating websites, apps for MSM (Grindr and PlanetRomeo), and gay media (Attitude, Winq.nl, and GayNews). The Ethics Committee of the Faculty of Social and Behavioral Sciences, Utrecht University approved this study (FETC17-131).

Sample

In total, 6,205 MSM were eligible (and consented). Because this study focused on HIV testing behavior among MSM at risk for HIV, HIV-positive MSM (n=360) were excluded from the analysis dataset. MSM with incomplete data (n=2,030) on sociodemographic, sexual practices, and social environmental factors were further excluded from the dataset. Excluded versus included respondents were compared using Chi Square analyses. Excluded respondents were more often non-Dutch and self-identified as bisexual. (Supplement 1). The total sample in the data analyses was 3,815 MSM.

Measures and coding

The questionnaire included reported HIV testing, socio-demographics, sexual risk behavior, social network characteristics, and behavioral constructs. The outcome variable for this study was HIV testing. This was defined as (1) not recently tested (longer than 1 year ago), (2) never tested, and (3) recently tested (within the last year), which was the reference group. We explored the following factors as covariates in the univariate and multinomial analyses:

(1) General socio-demographics, such as urbanization. Urbanization was categorized into highly urban (>2,500 living addresses/km^2) and non-highly urban (≤2,500 living addresses/km^2) based on the 4-digit postal code of where the MSM were living, and data from Statistics Netherlands (https://www.cbs.nl/en-gb). The non-highly urban category included middle-highly urban (1,500–2,500 living addresses/km^2), middle urban (1,000–1,500 living addresses/km^2), middle-low urban (500–1,000 living addresses/km^2), and low urban (>500 living addresses/km^2). General sociodemographic factors further include other factors, such as age (<25 years, between 25 and 42 years, >42 years), education level (low, medium/high), and ethnicity (Dutch, Western, Non-Western).
(2) Sexual risk-related factors, such as self-identification (homosexual and bisexual), condomless anal intercourse (yes, no), number of sex partners in the last six months (0-1, 2-5, >5), and ever being notified for HIV (yes, no).
(3) Social network characteristics, such as the share of gay friends in their social network, time spent with gay people, and sense of belonging to a gay community. Items on risk perception of getting HIV infected and perception of HIV severity, were also included. All the items were measured on a 5-point Likert scale (very low to very high). In the analyses, we categorized these into a binary factor: high (very high, high), and moderate-low (moderate, low, very low).

The questionnaire further included a question on the preferred method of HIV testing. For analyses, we categorized this into the self(sampling)test (including self-sampling and self-testing), GP, STI clinic, and Testlab (both sampling and testing at a laboratory of an STI clinic, without consulting the STI clinic staff), and no preference. Finally, the questionnaire included a question on the reason for not testing (in MSM who never tested). In the analyses, we grouped these into: no perceived HIV risk, having no HIV-related symptoms, expected stigma (afraid of test or the results, afraid of meeting people at the test location, the association of HIV testing with homosexuality, or unspecified), had the intention to test, but had not had the test, did not know where to test, and cost/logistics (long waiting times, too expensive).

Statistical analysis

Descriptive analyses were performed to determine the testing proportions and description of characteristics of MSM living in highly urbanized and non-highly urbanized areas. We assessed differences in HIV testing behavior by level or urbanization, using Chi square

tests, and univariate and multinominal logistic regressions (adjusting for confounders, i.e., the factors found to be associated with not (recent) testing in subsequent analyses). By evaluating the effect modification between urbanization level and the other previously mentioned factors, various effect-modification terms were found to be statistically significant ($P<0.05$). Therefore, the analyses were stratified according to urbanization level. We assessed the socio-demographics, sexual risk practices, and social environment factors for their association with HIV testing in univariable models, separately for MSM in highly and in non-highly urbanized areas, The statistically significant ($P<0.05$) factors obtained from the univariate analyses were included in backward multivariable multinomial logistic regression models, to assess the independent associations with recent HIV testing. Finally, we compared the preferred method of HIV testing of MSM living in high and non-highly urbanized areas and reasons for not testing for HIV (for MSM who have never tested), using Chi square testing. All analyses were performed using SPSS version 25.0 (IBM Inc., Somers, NY, USA). P values less than 0.05 were considered statistically significant.

Results

Of all the MSM in the analyses, 45.0% (1,718/3,815) lived in a highly urbanized area and 55.0% (2,097/3,815) lived in a non-highly urbanized area. The mean age was 36 years (standard deviation [SD]: 14.7), and 67.6% were highly educated. The characteristics are shown in Table 1 (highly urbanized areas) and Table 2 (non-highly urbanized areas).

Table 1. Factors associated with HIV testing for MSM living in highly urbanized areas from the multinominal regression analysis

		Total	Recently tested *(reference group)*	Not recently tested			Never tested		
		N	n (%)	n (%)	OR univariate	OR adjusted	n (%)	OR univariate	OR adjusted
Age (years)	<25	491	308 (62.7)	57 (11.6)	**0.47 (0.33-0.65)*** **	**0.29 (0.19-0.42)*** **	126 (25.7)	**3.51 (2.41-5.12)*** **	**2.54 (1.68-3.85)*** **
	25-42	668	498 (74.6)	136 (20.4)	**0.67 (0.52-0.90)*** **	**0.58 (0.43-0.79)** **	34 (5.1)	**0.59 (0.37-0.94)* **	**0.57 (0.34-0.93)* **
	>42	559	369 (66.0)	147 (26.3)	1	1	43 (7.7)	1	1
Education	Middle/Low	339	222 (65.5)	66 (19.5)	1.03 (0.76-1.40)		51 (15.0)	1.44 (1.02-2.04)	
	High	1,379	953 (69.1)	274 (19.9)	1		152 (11.0)	1	
Migration background	Dutch	1,307	871 (66.6)	276 (21.1)	**1.60 (1.10-2.33)* **		160 (12.2)	1.47 (0.93-2.32)	
	Western	157	112 (71.3)	26 (16.6)	1.17 (0.68-2.03)		19 (12.1)	1.36 (0.71-2.59)	
	Non-Western	254	192 (75.6)	38 (15.0)	1		24 (9.4)	1	
Self-identification	Bisexual/other	187	109 (58.3)	33 (17.6)	1.05 (0.70-1.58)	0.83 (0.53-1.30)	45 (24.1)	**2.79 (1.90-4.10)*** **	**1.75 (1.14-2.69)* **
	Homosexual	1,531	1,066 (69.9)	307 (20.1)	1	1	158 (10.3)	1	1
Sex partner <6 months	0-1	506	217 (42.9)	192 (37.9)	**9.53 (6.77-13.42)*** **	**11.93 (8.29-17.17)*** **	97 (19.2)	**14.18 ((8.37-24.01)*** **	**8.31 (4.79-14.40)*** **
	2-5	570	387 (67.9)	95 (16.7)	**2.65 (1.85-3.79)*** **	**3.10 (2.13-4.50)*** **	88 (15.4)	**7.21 (4.28-12.17)*** **	**4.94 (2.87-8.50)*** **
	>5	642	571 (88.9)	53 (8.3)	1		18 (2.8)	1	1
Condomless anal intercourse	No	711	423 (59.5)	156 (21.9)	**1.51 (1.18-1.92)** **	1.08 (0.82-1.42)	132 (18.6)	**3.31 (2.42-4.52)*** **	**2.50 (1.78-3.50)*** **
	Yes	1,007	752 (74.7)	184 (18.3)	1	1	71 (7.1)	1	1
Notified for HIV	Yes	686	419 (61.1)	163 (23.8)	**1.66 (1.30-2.1)*** **	**1.36 (1.04-1.78)* **	104 (15.2)	**1.90 (1.40-2.56)*** **	**1.73 (1.24-2.42)** **
	No	1,032	756 (73.3)	177 (17.2)	1	1	99 (9.6)	1	1
HIV severity [b]	High	1,413	949 (67.2)	287 (20.3)	1.29 (0.93-1.79)		177 (12.5)	**1.62 (1.05-2.51)* **	
	Moderate-low	305	226 (74.1)	53 (17.4)	1		26 (8.5)	1	
HIV risk perception [b]	Moderate-low	1,622	1,102 (67.9)	329 (20.3)	1.98 (1.04-3.78)*		191 (11.8)	1.05 (0.56-1.98)	
	High	96	73 (76.0)	11 (11.5)	1		12 (12.5)	1	
Amount of gay friends [b]	Moderate-low	1,067	682 (63.9)	221 (20.7)	**1.34 (1.04-1.73)* **		164 (15.4)	**3.04 (2.10-4.40)*** **	
	High	651	493 (75.4)	119 (18.3)	1		39 (6.0)	1	
Time spend with gay friends [b]	Moderate-low	1,219	789 (64.7)	251 (20.6)	**1.38 (1.05-1.81)* **		179 (14.7)	**3.65 (2.34-5.68)*** **	
	High	499	386 (77.4)	89 (17.8)	1		24 (4.8)	1	
Sense of belonging to a gay community [b]	Moderate-low	1,088	697 (64.1)	231 (21.2)	**1.45 (1.13-1.88) ** **		160 (14.7)	2.55 (1.78-3.64)***	
	High	630	478 (75.9)	109 (17.3)	1		43 (6.8)	1	

*P<0.05, **P<0.01, ***P<0.001

[a] Not included in the final model

[b] Measured on 5-point Likert scale

Table 2. Factors associated with HIV testing for MSM living in non-highly urbanized areas

		Total	Recently tested *(reference group)*	Not recently tested			Never tested		
		N	n (%)	n (%)	OR univariate	OR adjusted	n (%)	OR univariate	OR adjusted
Age (years)	<25	772	375 (48.6)	55 (7.1)	**0.29 (0.21-0.40)*** **	**0.16 (0.11-0.23)*** **	342 (44.3)	**3.08 (2.39-3.96)*** **	**1.96 (1.47-2.62)*** **
	25-42	607	378 (62.3)	155 (25.5)	0.81 (0.63-1.04)	**0.64 (0.48-0.85)** **	74 (12.2)	**0.66 (0.48-0.91)* **	**0.60 (0.42-0.85)** **
	>42	718	398 (55.4)	202 (28.1)	1	1	118 (16.4)	1	1
Education [a]	Middle/Low	897	474 (52.8)	176 (19.6)	1.07 (0.85-1.34)		247 (27.5)	1.23 (1.00-1.51)	
	High	1,200	677 (56.4)	236 (19.7)	1		287 (23.9)	1	
Migration background [a]	Dutch	1,828	986 (53.9)	374 (20.5)	**1.75 (1.08-2.85)* **		468 (25.6)	1.02 (0.71-1.48)	
	Western	106	68 (64.2)	17 (16.0)	1.16 (0.57-2.35)		21 (19.8)	0.67 (0.36-1.22)	
	Non-Western	163	97 (59.5)	21 (12.9)	1		45 (27.6)	1	
Self-identification	Bisexual/other	330	146 (44.2)	54 (16.4)	1.04 (0.74-1.45)	0.76 (0.53-1.10)	130 (39.4)	**2.22 (1.70-2.88)*** **	**1.70 (1.34-2.17)** **
	Homosexual	1,767	1,005 (56.9)	358 (20.3)	1	1	404 (22.9)	1	1
Sex partner <6 months	0-1	815	255 (31.3)	237 (29.1)	**7.40 (5.35-10.25)*** **	**8.72 (6.10-12.46)*** **	323 (39.6)	**12.45 (8.84-17.53)*** **	**7.02 (4.86-10.16)*** **
	2-5	715	434 (60.7)	117 (16.4)	**2.15 (1.53-3.01)*** **	**2.45 (1.73-3.54)*** **	164 (22.9)	**3.71 (2.62-5.27)*** **	**2.60 (1.80-3.76)*** **
	>5	567	462 (81.5)	58 (10.2)	1	1	47 (8.3)	1	1
Condomless anal intercourse	No	901	384 (42.6)	205 (22.8)	**1.98 (1.57-2.49)*** **	1.23 (0.95-1.60)	312 (34.6)	**2.81 (2.27-3.47)*** **	**1.70 (1.34-2.17)*** **
	Yes	1,196	767 (64.1)	207 (17.3)	1	1	222 (18.6)	1	1
Notified for HIV	Yes	992	484 (48.8)	219 (22.1)	**1.56 (1.25-1.96)*** **	**1.44 (1.12-1.85)** **	289 (29.1)	**1.63 (1.32-2.00)*** **	**1.69 (1.34-2.14)*** **
	No	1,105	667 (60.4)	193 (17.5)	1	1	245 (22.2)	1	1
HIV severity [b]	High	1,742	922 (52.9)	365 (21.0)	**1.93 (1.38-2.70)*** **	**1.72 (1.19-2.47)** **	455 (26.1)	**1.43 (1.08-1.89)* **	0.94 (0.68-1.31)
	Moderate-low	355	229 (64.5)	47 (13.2)	1	1	79 (22.3)	1	1
HIV risk perception [b]	Moderate-low	1,982	1,059 (53.4)	402 (20.3)	**3.49 (1.80-6.78)*** **	1.89 (0.95-3.79)	521 (26.3)	**3.48 (1.93-6.28)*** **	**2.08 (1.08-4.00)* **
	High	115	92 (80.0)	10 (8.7)	1	1	13 (11.3)	1	1
Amount of gay friends [b]	Moderate-low	1,521	748 (49.2)	314 (20.6)	**1.73 (1.34-2.23)*** **	**1.61 (1.21-2.15)** **	459 (30.2)	**3.30 (2.51-4.33)*** **	**2.03 (1.50-2.74)*** **
	High	576	403 (70.0)	98 (17.0)	1	1	75 (13.0)	1	**1**
Time spend with gay friend [a,b]	Moderate-low	1,756	905 (51.5)	370 (21.1)	**2.40 (1.69-3.39)*** **		481 (27.4)	**2.47 (1.80-3.39)*** **	
	High	341	146 (72.1)	42 (12.3)	1		53 (15.5)	1	
Sense of belonging to a gay community [a,b]	Moderate-low	1,532	780 (50.9)	325 (21.2)	**1.78 (1.36-2.32)*** **		427 (27.9)	**1.90 (1.49-2.43)*** **	
	High	565	371 (65.7)	87 (15.4)	1		107 (18.9)	1	

*P<0.05, **P<0.01, ***P<0.001

[a] Not included in the final model

[b] Measured on 5-point Likert scale

HIV testing by level of urbanization

Of all MSM, 19.7% (752/3,815) were tested, but not recently, 19.3% (737/3,815) were never tested, and 61.0% (2,326/3,815) were recently tested within 1 year. The proportion never tested was higher for MSM living in non-highly urbanized areas (25%) than in highly urbanized areas (12%) ($P<0.001$) (Table 3). The proportion recently tested was higher in MSM in highly urbanized areas than in MSM in non-highly urbanized areas. The level of urbanization was independently associated with recently tested and never tested. The proportion never tested was higher in MSM in non-highly urbanized areas than in MSM in highly urbanized areas. The proportion not recently tested did not differ by level of urbanization.

Table 3. HIV testing among MSM living in different urban areas in the Netherlands

	Recently tested N (%)	Not recently tested N (%)	Never tested N (%)	Recently tested Odds Ratio (95%CI)	Recently tested Adjusted Odds Ratio^ (95%CI)	Not recently tested Odds Ratio (95%CI)	Not recently tested Adjusted Odds Ratio^ (95%CI)	Never tested Odds Ratio 95%CI)	Never tested Adjusted Odds Ratio^ (95%CI)
Highly urbanized	1,175 (68.4)	340 (19.8)	203 (11.8)	1	1	1	1	1	1
Non-highly urbanized	1,151 (54.9)[+]	412 (19.6)	534 (25.2)[+]	**0.56 (0.49-0.64)** ***	**0.75 (0.64-0.87)** ***	0.99 (0.84-1.16)	0.87 (0.2-1.04)	**2.55 (2.14-3.04)** ***	1.89 (1.55-2.31)***
Middle-high	519 (55.3)	179 (19.1)	240 (25.6)	0.57 (0.49-0.67) ***	0.74 (0.61-0.89) **	0.96 (0.78-1.17)	0.86 (0.69-1.08)	2.57 (2.09-3.16) ***	1.94 (1.54-2.44) ***
Middle	262 (53.6)	105 (21.5)	122 (24.9)	0.53 (0.44-0.66) ***	0.73 (0.57-0.92) **	1.11 (0.87-1.42)	0.96 (0.73-1.26)	2.48 (1.93-3.19) ***	1.79 (1.34-2.37) ***
Middle-Low	200 (54.6)	69 (18.9)	97 (26.5)	0.56 (0.44-0.70) ***	0.76 (0.59-0.99) *	0.94 (0.71-1.26)	0.83 (0.60-1.14)	2.69 (2.045-3.54) ***	1.88 (1.37-2.57) ***
Low	170 (55.9)	59 (19.4)	75 (24.7)	0.59 (0.46-0.75) ***	0.78 (0.59-1.04)	0.98 (0.72-1.33)	0.78 (0.55-1.10)	2.44 (1.81-3.30) ***	1.92 (1.37-2.69) ***
Total	2,326 (61.0)	752 (19.7)	737 (19.3)						

*P<0.05, **P<0.01, ***P<0.001; in univariate and multivariable logistic regression analyses

[+] Proportion statistically significantly different from proportion in MSM in highly urbanized areas, using chi-square test; P<0.001

^models included age, education, migration background, self-identification, number of sex partners, condomless anal intercourse, notified for HIV, HIV severity, HIV risk perception, number of gay friends, time spent with gay friends, sense of belonging to a gay community.

MSM living in highly urbanized area

The results of the univariate analyses are presented in Table 1. In the multivariable analyses, factors for not *recent testing* (versus recent testing) were having 0–1, or 2–5 sex partners in the past six months (versus >5), and ever being notified for HIV, and inversely associated with age below 43 (versus above 42) (Supplement 2).

From the multivariable analyses, factors associated with *never testing* (versus recent testing) were age <25 years (versus age > 42 years), self-identification as bisexual (versus homosexual), having 0–1, or 2–5 sex partners in the past six months (versus >5), no condomless anal intercourse in the past six months, ever being notified for HIV, and inversely associated with age between 25 and 42 years (versus age >42 years).

MSM living in non-highly urbanized area

The results of the univariate analyses are presented in Table 2. From the multivariable analyses, factors associated with *not recent testing* (versus recent testing) were: having 0–1, or 2–5 sex partners in the past six months (versus >5), ever being notified for HIV, high HIV severity perception, and reporting a lower share of gay people among friends, and inversely associated was age <43 years (versus age >42 years) (Table 2).

From the multivariable analyses, factors associated with *never testing* (versus recent testing) were age <25 years (versus age >42 years), self-identification as bisexual (versus homosexual), having 0-1, or 2-5 sex partners in the past six months (versus >5), no condomless anal intercourse in the past six months, ever being notified for HIV, a lower HIV risk perception, and reporting a lower share of gay people among friends and inversely associated was age between 25 and 42 years (versus age >42 years).

Preferred method of HIV testing

In both highly urbanized and non-highly urbanized areas, MSM who recently or not recently tested, preferred testing at the STI clinic (figure 1). Of the MSM who never tested, the proportion who would prefer self-sampling or a self-test was 40.4% in non-highly urbanized areas and 35.0% in highly urbanized areas. Of the MSM who never tested the proportion who would prefer testing at the STI clinic was 32.0% in non-highly urbanized areas and 42.9% in highly urbanized areas.

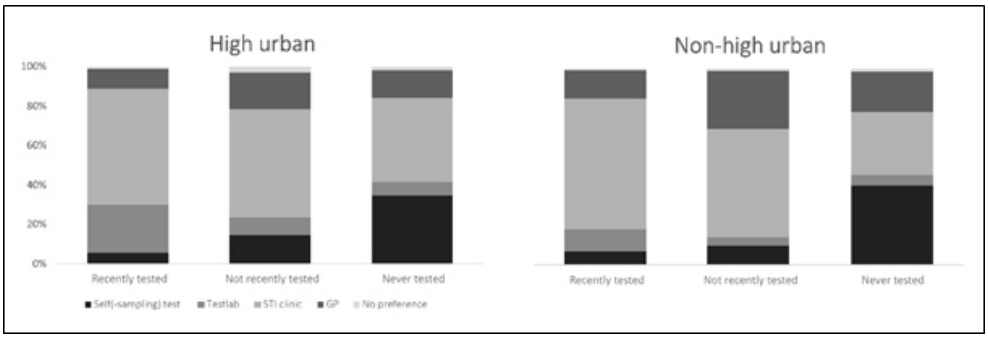

Figure 1. Self-reported preferred method of HIV testing for MSM living in different urbanized areas with different HIV test frequencies

Discussion

This study assessed the HIV testing behavior of MSM living in highly and non-highly urbanized areas in the Netherlands in 2018.

The proportion of MSM who never tested was higher in non-highly urbanized areas than in highly urbanized areas (25% versus 12%). This proportion is similar in other international studies in MSM outside major cities [14, 15]. The proportion of MSM who were not recently tested (tested > 12 months ago) was similar (20%) between non-highly and highly urbanized areas.

Factors associated with both never testing and with not recent testing and observed both in MSM in non-highly and MSM in highly urbanized areas were a lower number of sex partners in the past six months and never being notified for HIV risk. In addition, never testing in highly and non-highly urbanized areas was associated with age < 25 years, with self-identification as bisexual (versus homosexual) and with no condomless anal intercourse in the past six months. Finally, some additional factors were found to be associated only in non-highly urbanized areas, that is, a high HIV severity perception (associated with not recent testing), low HIV risk perception (associated with never testing), and reporting having a low share of gay people among friends (associated with both never testing and with not recent testing).

Several studies among showed MSM reporting low perceived risk as a reason for not being tested for HIV [16-18]. Low risk perception towards contracting HIV could be related to cause people can feel 'invincible' about contracting the virus [19]. However, perceived risk does not always represent actual risk. Adequate knowledge or talking about HIV/AIDS was found to be lower in some studies in non-high urbanized areas. Therefore, addressing realistic perceptions of behavior, vulnerability, and risk as well as knowledge on HIV and test-options, remains important to reach key populations for HIV testing.

People living in low urbanized areas are more likely to experience higher levels of HIV-related stigma. The expected stigma from the public community might hamper location-based testing [15]. Self-sampling strategies, in combination with social network testing (where tests are provided by a trusted other), have been proposed to overcome such barriers to testing. Self-sampling strategies provide autonomy and privacy and could potentially work especially well to reach MSM living in non-highly urbanized areas [20]. The distribution of self-sampling tests via the social network, for example by gay friends, has been shown to increase test uptake [21]. In a study among black MSM, receiving social support from peers in their social network was associated with a lower risk of delayed HIV testing. Social network interventions reach the people in the network, and individuals who are peer-related to them, which tend to make social network interventions cost-effective [22]. Its use in areas with potentially less strongly connected social networks, possibly non-highly urbanized areas, should be explored. The proportion of MSM reported to have a high share of gay friends was 37.9% (651/1067) in highly urbanized areas and lower with 27.5% (576/2097) in non-highly urbanized areas. A lower share of gay people among friends was associated with not testing or with not recent testing. It is possible that an increased non-hetero normative environment could contribute to HIV testing, with MSM role models who also test, and a positive norm for sharing information, and also to reduce stigma-related experiences. Social approval and emotional support can help to overcome perceived fear and stigma related to planning on HIV testing [19].

Various options are available for MSM to test for HIV in the Netherlands, for example, testing at STI care facilities, GP, and using self-testing/self-sampling. In our study, a substantial proportion of MSM in both non-highly and highly urbanized areas preferred the STI clinic for HIV testing; although MSM living in non-highly urbanized areas who never tested showed a slightly higher preference for self-testing/self-sampling. Testing using self-collected samples and in the home-setting (home-sampling) can remove structural barriers of HIV testing, such as being seen at a testing facility clinic or having to disclose sexual preference or

behavior and increase testing frequency [23]. In lower urbanized areas previously identified barriers, such as distance to clinic, and long waiting times [24]. Home-sampling tests could also serve healthcare providers by unburdening them. GPs working in smaller areas found it more difficult to discuss patients' sexual relationships than those working in urban areas [25]. However, implementation of home-sampling can be challenging. Barriers to implementing self-testing/self-sampling are related to costs, availability of a logistical infrastructure, and concerns related to the dislocation of self-testing/self-sampling from sexual health care pathways and services [23, 26, 27]. Coronavirus disease 2019 (COVID-19) has spread rapidly around the world, making care at home more important than ever, due to quarantine obligations and reduced access to routine location-based HIV testing.

Strengths and limitations

This study, with data from many MSM (n=3,815) living in the Netherlands provided insight into HIV testing among Dutch MSM living in different urbanized areas. This information is useful for sexual healthcare providers to optimize care and know which group does not get tested (on a regular basis). The collection of a wide range of sociodemographic, sexual risk behavior, and social environment factors enabled comprehensive explorative data analyses, with adjustment for confounding factors.

The validity of self-reported HIV testing behavior, recall bias, or social desirability bias could have occurred. This could possibly lead to an overestimation of actual testing behavior or an underestimation of sexual risk behavior. However, as the questionnaire was online and anonymous, we expect this bias to be likely to be small, and we do not expect this bias to differ between MSM from highly and non-highly urbanized areas. Some bias might also be introduced because of a probable overrepresentation of MSM with a high educational level, which occurs in most internet surveys. This study provides insight into HIV testing behavior among Dutch MSM, and might be similar for other countries and could provide insight into testing behavior in a large portion of the European population. Other parts of the world may have different living addresses/km^2 values for the classification of highly and non-highly urbanized areas. This could also be a possible explanation why in other studies transportation and logistics (e.g., distance to the clinic) were barriers for not HIV testing for MSM living in non-highly urbanized areas [28], but not in our study.

Implications & conclusions

HIV testing proportions and factors associated with never testing and not recent testing were found to differ between MSM in highly and non-highly urbanized areas of the Netherlands. Therefore, HIV-testing strategies should be targeted to reach MSM in different urbanization-settings. Home sampling might be a promising enhancement of current sexual health care for MSM. As implementation (e.g., providing a logistical infrastructure) for home-sampling and self-testing can be challenging, research is needed to determine the requirements for this process as well as the specific challenges associated with the areas in which implementation will take place.

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CHAPTER 5

Systematic development of an intervention to promote self-sampling for HIV and sexually transmitted infections for men who have sex with men: an intervention mapping approach

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Abstract

Sexual healthcare aims to reduce HIV and sexually transmitted infections (STI) by promoting testing and prevention. To better reach men who have sex with men (MSM), additional strategies are needed. Here we describe development of an intervention, which is part of a broader HIV/STI home-care program, targeted to reach MSM and motivate them to use self-sampling tests. Self-sampling includes blood sampling (finger prick) for HIV, hepatitis B and syphilis, and a urine sample, oral and anorectal swab samples for chlamydia and gonorrhea.

Intervention mapping, a systematic six-step approach, was used to guide the development process: 1.Needs assessment including interviews with MSM, 2.Create a matrix of change, 3.Selection of theory-based methods and practical strategies, 4.Intervention development, 5.Implementation plan, and 6.Evaluation (not included in this paper). Stakeholders were involved to increase program support and feasibility.

The needs assessment revealed that testing barriers among MSM related to stigma, time, and privacy concerns. Barriers among healthcare providers related to time, competing priorities, lack of expertise, and guideline restrictions. Included intervention components are designed to overcome these barriers, e.g. engaging role models, with a website with a role model story, and providing tailored information. Methods to reach MSM were a variety of information channels (posters, flyers, and audio-visual displays) and delivery modes, such as advertisements on websites, and invitational cards (online and paper) distributed by healthcare providers and MSM themselves (social network-testing/peer-testing).

Our intervention aims to encourage MSM to engage in testing, re-testing and providing a test to peer MSM. Evidence-based methods to overcome barriers were included to reach and motivate an increased number of MSM. Using Intervention Mapping stimulated systematic evidence based decision making and adapting the intervention to the target audience and setting. The next step (step 6) is to implement and evaluate the intervention.

Background

Men who have sex with men (MSM) are at increased risk of acquiring human immunodeficiency virus (HIV) and sexually transmitted infections (STI) [1]. In the Netherlands, the majority of newly-diagnosed HIV-infections are among MSM [2, 3]. Among MSM visiting Dutch STI clinics, 0.3% were diagnosed with HIV and 21.2% were diagnosed with an STI (including HIV) in 2019 [2]. HIV/STI testing and early linkage to care are critical for improving long-term individual health outcomes [4, 5]. Lack of (timely) HIV/STI testing introduces concerns for individual health, as well as public health concerns, in terms of ongoing transmission and adverse health outcomes. To reduce the number of new HIV and STI infections, timely testing, treatment and prevention is key. International guidelines for HIV/STI management recommend that all sexually active MSM are tested at least annually for HIV and all other relevant STIs: syphilis, hepatitis B (HBV), and anorectal, genital, and oropharyngeal infections of Neisseria gonorrhoeae (NG) and Chlamydia trachomatis (CT) [1, 6]. In the Netherlands, MSM can get tested at sexual healthcare centers (STI clinics), which deliver comprehensive sexual healthcare including free-of-charge testing for HIV, HBV, syphilis, and (extra)genital bacterial STI, STI treatment, HIV care referral to the hospital HIV treatment centre, partner notification, and sexual health counselling. MSM can also get tested at the general practitioner (GP) for HIV and STIs.

However, in spite of numerous public health efforts to promote HIV/STI testing and prevention, many MSM are not reached with high quality care and remain untested or not regularly tested; this leaves HIV/STI infections untreated [2, 3]. In the Netherlands, among MSM visiting STI clinics, only 18.9% test every 6 months for HIV/STI [7]. The statistics in our region (South Limburg, the Netherlands) are as follows: 28% of all MSM never tested before, 67% of young (<25 years) MSM never tested before, and only 20% tested regularly at the STI clinic [8]. Several barriers to getting tested among MSM have been identified in previous studies, including expected stigma from healthcare providers or laboratory staff who the MSM would need to see, fear of the potential consequences of a positive test result, lack of time to attend care, privacy concerns such as fear of being recognized at the STI clinic by other people, low-risk perception, and lack of motivation to be tested [9-13].

Therefore, additional care strategies to reach MSM with HIV/STI tests need to be explored. Alternatives to face-to-face clinic testing include 1) self-testing, where MSM collect their specimen, performs a test and interprets the test result in private, or 2) self-sampling,

where MSM collect their specimen in private, send their specimens to a laboratory where they are tested, and the laboratory returns the test result for HIV and STIs [14]. Self-collected samples may include urine, blood or saliva, or an oropharyngeal or anorectal swab. Reliable self-tests, showing direct test-results, are available for HIV, but are lacking for other STIs. Self-sampling (thus with accurate laboratory testing) can be performed at a person's home, which is also referred to as home-sampling. Self-sampling for urogenital and for extragenital NG and CT is comparable with clinician-administered samples [15-17].

Self-sampling for HIV/STI at home, additional to clinic-based testing, is expected to improve test uptake in MSM, has the potential to reach people who would otherwise not get tested, and serve as an entry point into HIV/STI prevention and care [18-21]. Self-sampling can potentially overcome barriers posed by in-clinic, face-to-face testing, such as fear of being seen at the clinic, expected stigma or long waiting times [21, 22]. Self-sampling in the home setting could work especially well in more rural regions, as people living in these areas may face environmental barriers, such as transportation constraints [23]. Home-based HIV/STI testing was found acceptable and convenient by MSM and can make testing easy, and time- and place-independent [24, 25]. Self-sampling tests were also found acceptable by healthcare providers, as they acknowledged the speed of home-sampling, the reduced workload of staff, and more privacy and confidentiality towards the patients when using self-sampling [18, 26, 27]. Although the potential benefits of self-sampling have been well-described, home-sampling has not been widely implemented in regular sexual healthcare and is currently not widely used by MSM. A recent study among MSM in Europe showed that knowledge of the existence of self-sampling for HIV is relatively low (25%), and actual use is very low (1%) [28]. During the COVID-19 pandemic, with the closing or more limited availability of physical testing locations, the demand for care at home has surfaced even more [29, 30]. Regional data from China and Australia indicated that the number of MSM undergoing facility-based HIV testing reduced by more than half during the COVID-19 pandemic [30, 31].

Systematically designing a healthcare program to promote healthy behavior (here: getting tested for HIV/STI) is essential for an effective implementation and wide uptake of the healthcare program. An intervention developed based on theory and evidence, and together with the target group and implementers of the intervention, is likely to be effective and sustainable [32, 33]. Intervention mapping (IM) is a health promotion protocol for selecting and applying social and behavioral science theories, to the planning, implementation and evaluation of health promotion interventions [33]. Disease prevention interventions that

have used IM have generally reported significant increases in the uptake of disease prevention programs [34]. Intervention mapping is a six-step approach that can be used to guide a systematic development of interventions based on theory and evidence. In step 1, a needs assessment is performed. In step 2, performance and change objectives are formulated based on knowledge gained in step 1. In step 3, theory-based intervention methods are selected to create change of the determinants of the behavior. In step 4, program components and specific materials are selected. In step 5, a plan for implementation of the program is made Step 6, the implementation and evaluation, is beyond the scope of this article and will be described separately, after the intervention has been implemented.

The aim of this study is to describe the systematic development, according to the IM protocol, of an evidence-based intervention to reach MSM and encourage them to undergo regular testing for HIV/STI with self-collected home-sampling tests. This intervention is part of a broader new home-care program that provides MSM with high-quality home-sampling tests for HIV and STIs and sexual healthcare.

Methods

The intervention described in this paper is part of a broader home-care program for MSM. This home-care program, includes a kit with sampling materials for 1) blood sampling (used for HIV, syphilis and hepatitis B testing), 2) urine sampling (used for genital NG and CT testing) and 3) extragenital sampling (swabs used for oropharyngeal and anorectal NG and CT testing). The sampling kits are returned by postal mail for laboratory testing. The home-care program is integrated in existing healthcare networks between different sexual healthcare providers and aims to engage MSM in HIV/STI testing, treatment, and care. This program also addresses sexual health and prevention strategies, such as condom use, PrEP and partner notification, and active follow up for individuals who test positive for HIV/STI to ensure they are engaged in care. The program is regional-focused and is designed for the province of Limburg, Southwest of the Netherlands. As part of the home-care program, we developed a strategy (the intervention) to promote the use of self-sampling tests. The framework for intervention development will be described in this method section and the application of this framework to design the intervention components is described in the results section.

Before the development of the intervention, a planning group of 12 people was established. A brief stakeholder assessment was done to explore who is potentially affected by the intervention and which stakeholders and experts from different disciplines and sectors should be included in the planning group. The planning group consisted of public health experts from the STI clinic of the public health service South Limburg, who were the initiators of the intervention, behavior change experts, and other stakeholders (decision-makers and potential intervention implementers) in care practice. The stakeholders included STI clinic and HIV treatment center care providers (nurses and physicians), a GP, laboratory staff, and STI clinic policy makers. Stakeholders were involved to increase support, feasibility, and success of the intervention [33, 35]. Public health experts were responsible for the intervention's development and will oversee the implementation of the intervention in a later stage. Healthcare providers shared their expertise on the target population, practice, and feasibility of new ideas. Behavior change experts shared their expertise on psychology and behavior change. Together, the planning group set a shared goal of promoting HIV/STI testing among MSM living in the area of study (region of Limburg) in the Netherlands who do not get regularly tested. Regular meetings with group members were held to discuss possible strategies to achieve the project goal and development progression.

Step 1: Needs assessment (logic model of the problem)

The first step of IM, a needs assessment, identifies the problem and determines what personal and environmental factors are related to the problem. In this article, we address the personal factors associated with MSM who do not (regularly) test for HIV/STI. Step 1 provides clarity on what should be changed and what the context for the intervention is, such as the population and setting. We conducted a literature search on the setting in which the intervention will be implemented, barriers preventing MSM from getting tested for HIV/STI, and on the methods that facilitate testing (self-sampling). Results from the literature search are embedded in the introduction.

Next, semi-structured, face-to-face interviews lasting 20-50 minutes were conducted among MSM to identify specific barriers to HIV/STI testing and to determine an effective and feasible method to enhance self-sampling HIV/STI tests. Interviewers were trained and guided prior and during administering interviews by the same supervisor. Eighteen MSM of eighteen years and older (mean age was 32 years) were recruited from a STI clinic (GGD Zuid Limburg) and Dutch lesbian, gay, bisexual, and transgender support organization (COC Maastricht) based on convenience sampling. Participants were asked to provide their ideas

and opinions about self-sampling at home, and the logistic procedure of these tests, such as receiving and returning the tests and on stimulating others to use self-sampling tests. Interviews were analyzed using qualitative analysis methods and QualiCoder software (Under development- Greater Good, Maastricht, the Netherlands). Statements that were mentioned more than once by participants were identified as a code. The codes were grouped into broader thematic concepts, such as attitudes, perceived barriers, preferences, experiences, personal ideas, outcome expectations, and self-efficacy of participants towards home-sampling test for HIV/STI. Ethical approval for the interviews was obtained from the Ethical Committee Psychology of Maastricht University (ERCPN 04_09_2012_S6). Written consent was obtained from the participants before the start of the interview.

Step 2: Intervention outcomes and objectives (logic model of change)

After the intervention goal was specified, objectives were formulated at the behavioral level to achieve the goal of MSM getting tested. These specific objectives are called performance objectives (PO). Then for each PO, the behavioral determinants derived from theoretical frameworks were selected based on importance (contribution to the behavior) and changeability, which was assessed by the planning group. A principled system of importance of themes was used by the planning group, guided by the current STI/HIV diagnosis and treatment guidelines for STI/HIV sexual health care in our country. Selection of determinants was guided by literature, information gained from interviews (the needs assessment), and expert advice from the planning group. Finally, the PO and their behavioral determinants were combined to create matrices of change objectives (COs), to identify what should be targeted by the intervention. Each CO was formulated to be measurable and action-oriented.

Step 3: Intervention design

Using the results of the needs assessment in step 1 and the matrix of change created in step 2, theory-based intervention methods were selected to address the determinants selected in step 2 to promote behavior change.

For each determinant and CO, a theoretical method for influencing changes in the behavioral determinants was selected. Methods were selected based on literature and expert advice of the planning group members, taking into account the target population, feasibility, and changeability of the determinants. Behavior change experts shared their opinions and experiences regarding the methods that could be used to effectively promote behavior change.

Next, every method was converted into a practical application, which is a specific technique for the practical use of theoretical methods in ways that fit with the target group and the context in which the intervention will be conducted. The experts from the planning group converted these methods into practical applications by taking into account the target group, parameters for effectiveness of the selected methods, and the results of the needs assessment performed in step 1 [33]. STI clinic and HIV treatment center care providers shared their opinions and experiences regarding the applications that were likely to be feasible and fit the target group.

Step 4: Intervention production

The practical applications were combined into intervention components. Again, both implementers (care providers) and representatives of the target group (MSM) of the intervention were involved and consulted in the process. Members of the planning group were asked to share their opinions and experiences during brainstorm meetings to select the best possible intervention design for the target group, to increase the likelihood that the intervention would be used properly, and would reach the set goal. This step also involves an assessment of whether the intervention components and materials will be feasible in terms of time and budget constraints and if the target group will be reached.

Step 5: Implementation plan

In the Netherlands, MSM can be tested for HIV/STI at STI clinics, GP offices, and HIV treatment centers. Therefore, the intervention was intended to be implemented by healthcare providers at these locations. Public health experts, who are responsible for the development of the intervention, also guided and oversaw the implementation of the intervention. To maximize implementation, key stakeholders were engaged in the development and implementation process.

In order to prepare for implementation of the intervention, information regarding the implementers' needs and barriers to the delivery and promotion of HIV/STI testing among MSM was first gathered through an exploratory literature search, expert opinion, and semi-structured face-to-face interviews with 19 healthcare providers from the STI clinic of the public health service South Limburg and HIV treatment center Maastricht. Participants of the interview were potential implementers of the intervention and were included based on convenience sampling. With the information obtained from this needs assessment, a plan was

made for adoption, implementation, and management of the intervention in real-life contexts.

Results

Step 1: Needs assessment

The needs assessment was carried out in two steps: a literature search and additional qualitative research. The results from the literature search are embedded in the introduction. Results showed that not all MSM are regularly tested for HIV/STI. Barriers for testing were mainly related to expected stigma, time and privacy concerns. Self-sampling tests have been proven feasible and effective for increasing HIV/STI testing.

The qualitative research consisted of interviews with members of the target group. The interviews with MSM (n=18) showed that self-collected home-sampling tests are considered to be highly acceptable. Home-sampling was judged as highly promising by MSM to overcome main barriers to getting tested. Interviewed MSM stated that these tests were perceived as time-efficient, reliable, convenient, easy, modern, and innovative. MSM mentioned it was important that the sampling could be conducted in the comfort of their own homes. Consequently, they appreciated not having to make the effort to travel to the health clinic and not having to wait for appointments. Participants appreciated that the self-sampling tests would lead to savings in money for gas and parking. Furthermore, some participants valued that they would not have to take time off from work and could use the sampling kit whenever it suited them best. Participants explained that these positive aspects increased the likelihood of them making the effort to get a HIV/STI test and therefore expected that they and possibly other MSM would use self-sampling if available. Several participants stated that they did not like sampling blood sample, which would be a possible barrier to use self-sampling. Furthermore, some participants were afraid that the sampling could be wrongly executed and thereby influencing the reliability of the tests. Also, concerns towards the lack of face-to-face counselling were raised.

Based on the findings from step 1, the needs assessment, a logic model of the problem was created (Figure 1) and the following program goal was formulated: MSM are tested using self-sampling for all relevant HIV/STI at all three relevant anatomic sites at least twice a year.

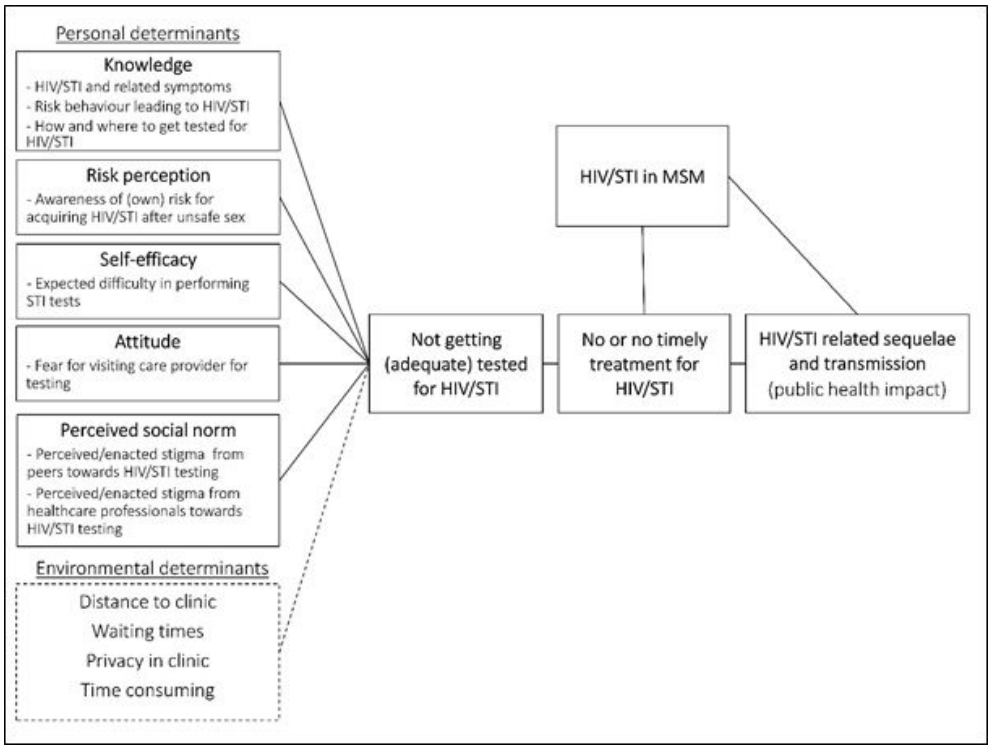

Figure 1. Logic model of the problem regarding lack of HIV/STI testing among men who have sex with men.

Step 2: Program outcomes and objectives

In order to reach the program goal that MSM get themselves tested for all relevant HIV/STI at all three relevant anatomic sites using self-sampling tests, six POs were formulated (Table 1). First, MSM decides to get tested (PO1). Second, MSM requests a sampling kit (PO2). Third, MSM performs sampling according to the instructions (PO3). Fourth, MSM should return the sampling kit (via postal mail) (PO4). If test results are positive, MSM should make an appointment for treatment (PO5) and complies with treatment (PO6). For each PO, determinants were selected. Determinants included knowledge, risk perception, self-efficacy/skills, attitude (cognitive/affective), and perceived social norms. For example, the most important and changeable determinants for PO1 were knowledge, risk perception, and perceived social norms (Table 1).

Next, for every PO and their determinants, a CO was formulated. For example, for PO3, "MSM uses sampling kit correctly according to the instructions" CO SE2, "Express confidence in ability to perform the test" was formulated to address the determinant self-efficacy. A matrix of change was made (Table 1).

Table 1. Performance and change objectives to promote HIV/STI testing with self-sampling tests among men who have sex with men (MSM)

	Knowledge	Risk Perception	Self-efficacy/Skills	Attitude (Cognitive/ Affective)	Perceived Social Norm
PO1. MSM decides to get tested	K1. Describe when it is necessary to go for HIV/STI testing	R1. Appraise personal risks of HIV/STI after unprotected sex			SN1. Acknowledge responsibility for own and partners' health
PO2. MSM requests a sampling kit	K2. State how and where you can order a sampling kit	R2. Appraise effects of HIV/ STI and personal risk	SE1. Express confidence in ability to order a sampling kit	A1. Acknowledge the advantages of using the sampling kit A2. Acknowledge the importance of getting tested	
PO3. MSM uses sampling kit correctly according to the instructions.	K3. State how to perform blood and urine sampling and how to perform extragenital swab sampling		SE2. Express confidence in ability to perform the test SK1. Able to demonstrate how to perform the test SK2. Able to formulate ways of dealing with negative emotions involved with testing	A3. Acknowledge emotions involved with testing (i.e., fear) A4. Acknowledge that the pros of testing outweigh the cons	
PO4. MSM returns sampling kit via mail	K4. List were and how you can return a sampling kit			A5. Acknowledge the emotions involved in the outcome (i.e., fear of a positive test)	
PO5. MSM makes an appointment for treatment	K5. Describe how to get treatment			A6. Acknowledge the importance of getting treatment	SN2. Acknowledge responsibility to get treated for HIV/STI
PO6. MSM complies with treatment	K6. Describe the treatment procedure		SE4. Express confidence in complying with treatment		SN3. Acknowledge responsibility to comply with the treatment protocol (i.e., no unsafe sexual contact during treatment)

Table 2. Examples of selected theoretical methods and applications used to get men who have sex with men (MSM) tested for HIV/STIs

Determinant	Change Objective	Parameters for Use	Method	Application
Knowledge	K1. Describe when it is necessary to go for HIV/STI testing	Tailoring variables to relevance	Tailoring	Information tailored to target group provided on printed flyers/posters
	K3. State how to perform blood and urine sampling and how to perform extragenital swab sampling	Schematic guides of what is to be learned	Advance organizers	Schematic test instruction with images on how to perform sample collection
Risk perception	R1. Appraise personal risks of HIV/STI after unprotected sex	Cognitive and affective appraisal of self-image	Self-reevaluation	High-risk behavior for acquiring a HIV/STI is described on flyer and poster
	R2. Appraise effects of HIV/STI and personal risk	Present messages as individual and undeniable	Personalize risk	Website contains a short questionnaire on risky sexual behavior, generating personal feedback on HIV/STI risk
Self-efficacy/skills	SK1. Demonstrate how to perform the test	Credible source	Verbal persuasion	Video instructions performed by role model on how to perform self-collected test
		Attention and identification with the model	Role models	
Attitude (cognitive/affective)	A1. Acknowledge the advantages of using the sampling kit	Attention and identification with the model	Role models	Role model story on website about self-sampling experience

Step 3: Program design

For each determinant selected in step 2, change objectives were formulated. For example, for the determinant knowledge, change objective K1 ("Describe when it is necessary to go for HIV/STI testing"), the method "tailoring" was chosen. When using tailoring, the intervention (components) will be adjusted to previously measured characteristics of participants of the target group. The method "tailoring," chosen to change the determinant knowledge about HIV/STI and HIV/STI testing, was transformed into a practical application of providing tailored information to fit the MSM target group by presenting healthcare information only relevant for men who have sex with men. Other examples of selected methods and applications are displayed in Table 2.

For each determinant and change objective, a theoretical method was selected. For example, self-efficacy is constructed from Social Cognitive Theory [36-38]. Perceived self-efficacy refers to beliefs in one's capabilities to organize and execute the courses of action required to achieve the desired change. Unless people believe they are able to achieve desired changes by their actions, they have little incentive to act or to persevere in the face of difficulties and setbacks. A way of creating and strengthening self-beliefs of efficacy is through experiences provided by social models [39].

Risk perception (perceived susceptibility), for example, comes from the Health Belief Model (HBM) [40, 41] and refers to the belief about the chances of being exposed to a certain health outcome, for example, being infected with HIV/STI [40]. The HBM theory suggests that people's beliefs about health problems, perceived benefits and barriers of action, and self-efficacy explain (lack of) health-promoting behavior. Interventions based on the HBM may aim to increase risk perception and perceived seriousness of a health condition by providing education about prevalence and incidence of disease, individualized estimates of risk, and information about the medical, financial and social consequences of disease [40]. The HBM contains several concepts that predict why people will take action to prevent, to screen for, or to control illness conditions; these include susceptibility, seriousness, benefits and barriers to a behavior, cues to action, and self-efficacy [40]. A construct of the HBM is a stimulus, or cue to action, which must be present in order to trigger the health-promoting behavior. Therefore, in our intervention we incorporated multiple stimuli in different stages in our intervention to promote MSM to use home-sampling to test for HIV/STI.

Step 4: Intervention production

The main intervention components developed by the planning group were a website, cards with an invitation to be tested, and different information channels (posters, flyers, and narrowcasts [audio-visual displays]).

To increase knowledge and awareness, different information channels for MSM were developed (posters, flyers, and narrowcast [audio-visual display]). Development was accomplished together with representatives of the target group and healthcare providers, in order for the intervention to fit the target group. MSM stated in the interviews that information on self-sampling tests should not only be displayed at specific venues for MSM (such as gay sauna's), but also in public places. Therefore, posters, flyers, and narrowcast will be displayed in relevant and healthcare departments (e.g., waiting areas at GPs' offices, schools, HIV treatment centers, and STI clinics) and contain short information on the importance of HIV/STI testing and a link to a website where sampling kits can be ordered. The posters, flyers, and narrowcast will serve as a stimulus to HIV/STI testing and to visit the website. Promotional materials will contain information on risk factors for acquiring HIV/STI, addressing the determinant "knowledge," in order to accomplish K1 ("Describe when it is necessary to go for HIV/STI testing"), which is a change objective from P01 ("Decides to get tested").

Previous studies have consistently shown that a person's self-efficacy and intention to test are key determinants of actual testing [42]. A person with low testing intention is unlikely to return the tests when tests packages are just given to him or her. Therefore, in our intervention, MSM will receive cards with an invitation to order a self-sampling kit online. Subsequently, MSM have to perform the action of going to a specifically designed website to order a sampling kit. On the website, there will be eligibility questions for MSM who want to order a test (for example, MSM can only request a test when residing in the region served by the implementing healthcare providers). MSM are also asked to fill in questions for care and evaluation purposes. Interviewed MSM stated that it would acceptable to go through these steps, as the free-of-charge home-sampling tests they subsequently receive will make this worth the effort. This website contains several elements that will increase MSM's self-efficacy and testing intention. The website will contain information about HIV/STI and how MSM can order a sampling kit. This website will also address testing barriers and will contain several methods to promote behavior change. First, information on the website about risk factors, HIV/STI, and testing presented on this website will be tailored to the needs of

MSM (method: tailoring). Second, there will be a short story of a male role model and his personal positive experience with home-sampling tests (method: role models). MSM stated in the interviews that a role model expressing a positive experience with home-sampling would encourages them to use a home-sampling test. Engaging MSM themselves as role models in HIV prevention strategies and peer-led intervention, have a greater improvement in knowledge of HIV and improving behavioral outcomes [43, 44].

In cases where MSM have ordered and received their sampling kit, but did not return it within 2 weeks, up to three text message reminders will be sent. The STI clinic will send tailored SMS reminders. Reminders (text messages) will be used to promote testing behavior, as reminders have proven to increase participation [45, 46]. The text messages will also give MSM the opportunity to contact the STI clinic if they want more information or have questions (for example about HIV/STI, self-sampling tests, drug use during sex: chemex or PrEP). Interviewed MSM were concerned of the lack of face-to-face counseling, therefore these text messages will give MSM the opportunity to contact healthcare providers in a accessible way.

To reach MSM who are not reached by healthcare providers or by the information channels used in the intervention (online advertisement and narrowcasts or as posters and flyers), an additional method (i.e. including the social network) was chosen to further facilitate HIV/STI testing by mobilizing social support. All MSM who use a self-sampling kit will be invited (via website, healthcare provider, etc.) to also offer a testing opportunity to their MSM peers. Sexual network characteristics are related to interconnectedness and concurrency of sex partners, facilitating HIV/STI spread. Members of the social and sexual networks surrounding those with (previous) HIV/STI infections are also at high risk of acquiring HIV/STI infections [47]. Furthermore, peers are more likely to influence behaviors of other MSM in their social network than professionals and thereby may be better able to connect to members of their social networks who are not linked to care. Peers and social network testing have therefore the potential to increase HIV/STI detection and testing behavior in networks of young people and MSM [42, 48-51]. Offering a HIV/STI self-sampling test has the potential to be awkward, and people who test for HIV/STI may fear being stigmatized by others if they were to disclose sensitive information or to distribute a test. However, interviewed MSM stated they would be willing to give a test (invitation) to their peers. Also, previous studies have shown that people effectively avoid being stigmatized by disclosing information [52] or distributing tests [42] only to "trusted peers". The friend is more likely to get

tested, because he or she received the test from a role model with a positive experience to testing. Moreover, peers may also consciously or unconsciously select the friends who are more at risk, which would also potentially increase the effectiveness of this method [53]. The role model on the website will also address peer-testing and will give some tips to open a conversation with peers about HIV/STI testing and offering the self-sampling test.

As people with a previous STI are more likely to become infected again (7%-20%) [54-56], healthcare providers (GPs, providers at HIV treatment centers, and STI clinic nurses and physicians) can actively offer a testing opportunity to MSM patients who previously had a STI. The patients will receive a text message with a link to the website and a unique code to order a home-sampling test.

Step 5: Implementation plan

Results of the interviews with implementers of the intervention (healthcare providers from HIV treatment centers and GPs) revealed that barriers in offering and addressing STI tests to MSM were mainly lack of time, competing medical priorities, lack of testing and treatment knowledge (expertise), discomfort with sexual history and genital examinations, patient reluctance, role reluctance (responsibility), and financial or guidelines restrictions [13, 57, 58].

Next, a collaborative infrastructure was established between regional healthcare providers from HIV treatment centers, GPs and STI clinics, implementers and planning group members that enables and facilitates information. This will support implementation and increase the likelihood of the intervention continuing. Because of its primary public health goal, and its responsibility in delivering high-quality HIV/STI care, the STI clinic is best suited to facilitate, manage, and organize the changes in process of care required from GPs, hospital care providers, and STI nurses and physicians.

The last step of the implementation plan will be to inform key care providers (e.g., heads of departments) about the program in a face-to-face meeting. They will play an active role in implementing the program in their department and in motivating their colleagues to use the program. These key persons serve as the contact person for their colleagues and for the public health experts (creators of the program). When implemented, regular evaluation and feedback meetings will be arranged between the public health experts and key persons in order to keep healthcare providers motivated and involved.

Discussion

We used IM to develop an intervention to promote HIV/STI self-sampling in MSM. The intervention is systematically based on theory and evidence and designed for practical application by healthcare providers in STI clinics, HIV treatment centers, and GPs' offices, to reach MSM and promote uptake of HIV/STI testing. The intervention consists of cards with an invitation for testing, and different offline and online information channels (posters, flyers, and narrowcasts [audio-visual displays]), a website and text message reminders to promote the use of HIV/STI self-sampling tests. This intervention will be part of a home-care program that combines home-based testing with complete care, offering counselling, treatment, retesting opportunities, and partner notification combined with eHealth in order to improve HIV/STI control in MSM.

The intervention consist of distributing invitations to test for HIV/STI via self-sampling kits. Offering a self-sampling testing opportunity yields higher testing rates compared with offering a testing opportunity at a clinic [21, 59]. As the invitation for testing will be distributed by various online and offline ways (via healthcare providers, social network, and via posters flyers and website advertisements) we try to maximize our reach with this intervention. In our intervention, we will employ the social network of an MSM who is currently in care or recently tested. Using the social network, gives an opportunity to reach MSM who are not reached with current healthcare and has the opportunity to increase social support and reduce perceived stigma around STI/HIV testing. In a study among black MSM, receiving social support from other black MSM friends was associated with lower risk of delayed HIV testing [51]. Social network-testing/peer HIV testing outside the healthcare setting is a possible way of increasing uptake of testing in high-risk groups [60].

In our intervention we use mobile text messages to 1) send reminders for MSM who have received a home-sampling tests, but did not completed the test and 2) send an invitation for retesting 6 months after testing positive for HIV/STI. Using mobile text messages is widely recognized as an effective communication method between healthcare professionals and their clients, and is increasingly accepted in healthcare setting. Studies with text message reminders have increased HIV/STI re-testing among MSM and other populations [61-63]. Mobile text message reminders are a cheap and efficient addition to increase participation and a low-threshold method for MSM to contact healthcare providers if needed.

In the development process, using IM stimulated the identification of specific determinants which influence behavior change. When using a structured protocol, it ensures that all relevant determinants are addressed. Combining expert opinions and theories made it clear which elements and program components would be most effective and should be included in an intervention. We experienced that using the IM protocol as described by the developers is potentially a lengthy process, requiring time (possibly more than what is available in the day-to-day practice) of sexual healthcare providers. This issue with using IM thoroughly and according to textbook instructions is also described by other authors [64, 65]. However, IM can also be applied in a condensed version, also serving as a highly valuable guide for development and may in some practical settings be a more feasible option. In our study, we did a condensed version of the needs assessment, interviews participants were selected based on convenience sampling and gathering expert advice was gathered in an informal setting. Although these thing could have been performed in a more elaborated structured way, we adapted this process so it fitted the needs and resources available in our practice-based development of this intervention. The use of both extended and condensed versions of the IM protocol has shown to be useful and effective for development of interventions among several public health domains, such as in promoting sexual health programs, cancer screening, and physical activity [66-69].

In our planning group we had the advantage of having behavior change and IM experts in our planning group, as sufficient theoretical knowledge and experience with technical IM aspects has to be available. Yet, the IM protocol is written in a clear steps, therefore the protocol can also be used for developers without previous behavioral change theory expertise. The protocol enhances a better understanding of the complexity of a behavior by breaking down behavior in understandable terms of performance objectives and underlying change objectives. Therefore, the use of IM when designing an intervention is feasible in a variety of settings. Using IM ensures that the intervention is adapted to the regional setting in which the intervention will be implemented, but is also useful for adapting an existing program from one population to another.

In our study, using IM facilitated the collaboration between intervention developers, implementers, stakeholdersand between different healthcare provider. This collaboration is a solid base for implementing the intervention and enhances patient sexual healthcare between different disciplines (STI clinic, HIV treatment centre, GP, laboratory staff). Overall, we feel that using IM has benefited our development process by serving as a guide for de-

velopment, ensuring there was a clear understanding of the problem and its determinants and ensuring there is a solid base for implementation of the intervention. Therefore, we would recommend other developers to use IM or another structured protocol for developing interventions .

Limitations

In our needs assessment, we interviewed MSM based on convenience sampling due to time and resource restrictions. These MSM where all familiar with sexual healthcare. Although these interviews give an insight in acceptance and preferences of using self-sampling among MSM, it would also be good to have this information available for MSM who are not familiar with regular sexual healthcare. Therefore, more research is needed on how to reach MSM who are currently not reached with care.

Expert advice was collected in a semi-structured way, i.e. mainly by brainstorm sessions, guided by structured list of themes that were deemed important a priori or were raised ad hoc). Collection of advice was done during several stages of the development process. As the information collection process was mainly informal, it is possible that a n over-representation of subset of perspectives and under-representation of others has occurred. However, as experts were from different disciplines and different backgrounds, different perspectives were taken into account.

This article focused on the personal behavior aspects of testing behavior. Although environmental conditions can influence health problems directly and indirectly through their influence on behavior, we did not describe determinants at the environmental level. However, with the developed program, several environment-related testing barriers (e.g., distance to the testing clinic and privacy issues in the building) may be mitigated by self-sampling at home [22, 23].

In this article, steps 1-5 of the intervention mapping protocol (development of the intervention) have been described. Step 6, evaluation of the intervention, will be conducted in the next phase. Implementation of the broader home-care program was pilot tested in a hospital setting, which allowed for a process evaluation to optimize the program and its implementation. This pilot focused on sustainable implementation, yielding valuable new scientific insights and practical information [46]. The full implementation of the home-care program, including this intervention, is currently ongoing.

Conclusions

This intervention to promote HIV/STI self-sampling testing among MSM was systematically developed for effective behavioral change. IM is a useful guide to develop interventions in practice for health promotion. In the program, evidence-based methods to overcome barriers are included to reach an increased number of MSM and motivate healthcare providers. The next step (step 6 of the IM approach) is to evaluate the adopted and implemented program. The clear documentation of the development process of an intervention could be very useful to other public health professionals who are developing healthcare programs.

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CHAPTER 6

Pilot implementation of a home-care programme with chlamydia, gonorrhoea, hepatitis B and syphilis self-sampling in HIV-positive men who have sex with men

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Abstract

Not all men who have sex with men (MSM) at risk for sexually transmitted infections (STIs) and human immunodeficiency virus (HIV) infection currently receive sexual healthcare. To increase the coverage of high-quality HIV/STI care for MSM, we developed a home-care programme, as extended STI clinic care. This programme included home sampling for testing, combined with treatment and sexual health counselling. Here, we pilot implemented the programme in a hospital setting (HIV-positive MSM) to determine the factors for the successful implementation of STI home sampling strategies.

Healthcare providers from the HIV hospital treatment centre (Maastricht) were invited to offer free STI sampling kits (syphilis, hepatitis B, [extra]genital chlamydia and gonorrhoea laboratory testing) to their HIV-positive MSM patients (March to May 2018). To evaluate implementation of the program, quantitative and qualitative data were collected to assess adoption (HIV care providers offered sampling kits to MSM), participation (MSM accepted the sampling kits) and sampling-kit return, STI diagnoses, and implementation experiences.

Adoption was 85.3% (110/129), participation was 58.2% (64/110), and sampling-kit return was 43.8% (28/64). Of the tested MSM, 64.3% (18/28) did not recently (< 3 months) undergo a STI test; during the programme, 17.9% (5/28) were diagnosed with an STI. Of tested MSM, 64.3% (18/28) was vaccinated against hepatitis B. MSM reported that the sampling kits were easily and conveniently used. Care providers (hospital and STI clinic) considered the programme acceptable and feasible, with some logistical challenges. All (100%) self-taken chlamydia and gonorrhoea samples were adequate for testing, and 82.1% (23/28) of MSM provided sufficient self-taken blood samples for syphilis screening. However, full syphilis diagnostic work-up required for MSM with a history of syphilis (18/28) was not possible in 44.4% (8/18) of MSM because of insufficient blood sampled.

The home sampling programme increased STI test uptake and was acceptable and feasible for MSM and their care providers. Return of sampling kits should be further improved. The home-care programme is a promising extension of regular STI care to deliver comprehensive STI care to the home setting for MSM. Yet, in an HIV-positive population, syphilis diagnosis may be challenging when using self-taken blood samples.

Background

Men who have sex with men (MSM) are at increased risk of acquiring human immunodeficiency virus (HIV) infections and sexually transmitted infections (STIs) [1]. STI continues to be a growing epidemic among MSM [2], particularly for those living with HIV. Integration of STI testing and control strategies with HIV testing and care is imperative to stop STI transmission at the population level and to enable optimal HIV/STI patient management [3].

Dutch national guidelines recommend the routine, i.e. up to four times a year [4] testing of HIV-positive MSM for syphilis, genital, anorectal, and oropharyngeal Neisseria gonorrhoea (NG) infections, for genital Chlamydia trachomatis (CT) infection, and, after self-reporting the symptoms of extragenital infection, receptive anal sex, or oral sex, for extragenital chlamydial infection [5]. However, not all MSM receive appropriate sexual healthcare services, despite testing guidelines and existing high-quality sexual healthcare [4, 6, 7]. For HIV positive MSM, STI test practice in HIV care is not always fully implemented [3] and is furthermore likely to miss extragenital chlamydia cases as these are frequently asymptomatic and frequently observed in the absence of reported anal sex [8]. For example, in a US HIV care hospital setting, STI screening in the hospital setting was only 2.0–8.5% [9].

In the Netherlands, STI clinics provide comprehensive sexual healthcare for MSM, which includes free-of-charge testing for HIV, hepatitis B (HBV), syphilis, and (extra)genital bacterial STI, STI treatment, HIV care referral to the hospital HIV treatment centre, partner notification, and sexual health counselling. HIV-positive people are treated at HIV treatment clinics. Here, care providers can also offer STI tests to their patients. However, there are no specific HIV (hospital) clinic guidelines that recommend routine STI screening for HIV positive MSM patients during regular HIV care visits; patients are tested only when they are considered at risk for STIs. MSM can also get tested at the general practitioner (GP) for STIs. Depending on the type of health insurance, MSM may have to pay for the visit and tests and GPs testing guidelines only recommend extragenital testing based on sexual history and reported symptoms.

Suboptimal STI testing of MSM in the HIV care setting has several barriers at the care provider level and patient level. For HIV care professionals, the following barriers are encountered when performing STI testing to MSM patients: insufficient funds for STI screening, competing priorities (insufficient time for STI testing), and professionals' uncomfortable

feeling when discussing patients' sexual practices [10, 11]. HIV-positive MSM may seek STI care outside the HIV clinic, including their general practitioner or an STI clinic, because of the following reasons: STI testing in an STI clinic is easier accessible compared to an HIV clinic, wanting to maintain anonymity, and more frequent testing can be performed in an STI clinic than in an HIV clinic [10].

To reach out to a significant number of MSM (HIV positive and HIV-untested and negative MSM) with comprehensive HIV/STI care, we recently developed a regional home-care programme, as an extension of regular STI clinic care. The programme encourages MSM to undergo HIV/STI testing and be treated, using home sampling for comprehensive testing on HIV (restricted to HIV-negative or untested MSM), HBV (restricted to unvaccinated MSM), syphilis, and anorectal, urogenital, and oropharyngeal CT and NG. The programme was systematically developed, in close collaboration with its users, according to the intervention mapping strategy, reported elsewhere (future reference), to address and overcome barriers to HIV/STI testing. Self-sampling at home (i.e. home sampling) is the central component of our programme as it has been proven to be an effective additional strategy to increase STI testing uptake [12, 13]. Self-sampling at home makes testing convenient, increasing patient autonomy, saving time for care providers, and decreasing barriers for MSM in undergoing regular testing and for providers in offering STI testing to their MSM patients. Professionals in HIV treatment clinics perceived home sampling tests as time-saving for providers, overcoming patient discomfort and enabling increased patient access to testing [14].

In our home-care programme, home sampling is combined with eHealth technologies, which means that semiautomatic and semi-tailored text messages methods are used to improve response and enable better patient management. A large body of evidence has emerged displaying the effectiveness of text messaging in HIV/STI control [15]. The programme offers high-quality regular STI clinic care, and testing is linked to STI treatment, HIV care referral, partner notification, and sexual health counselling. Our home-care programme is designed for implementation as extension to regular care in various sexual healthcare settings, including STI clinics, but also including general practices (GP), and hospital HIV treatment centres.

In this paper, we describe the pilot implementation of this newly developed home-care programme within the hospital setting of the HIV treatment centre. This study aimed to evalu-

ate this pilot implementation regarding its test usage and logistics and to reveal the experiences of the users (HIV-positive MSM) and implementers (hospital HIV treatment providers and STI clinic professionals). The findings will further aid in the optimisation of the programme and can provide further insights to sexual healthcare providers who intend to use home sampling strategies to improve the testing uptake in MSM.

Methods

Components of the home-care programme and implementation

Home sampling kits for CT, NG, syphilis, and HBV were offered by healthcare providers from the hospital HIV treatment clinic in Maastricht to their MSM patients when they routinely attended HIV care (March 2018 to May 2018), regardless of their STI testing history. Healthcare providers could offer a sampling kit to their HIV positive patients when they were 18 years or older, understood Dutch or English language, and ever had sex with men. When a patient accepted a sampling kit, his telephone number was documented because a text message reminder will eventually be sent to the patient once the sampling kit was not received by the laboratory within 2 weeks. When needed, a second reminder will be sent 2 weeks thereafter. After self-taking the samples and completing the accompanying online questionnaire, participants could return the samples to the laboratory for testing.

After the participants returned the self-taken materials and questionnaires, further patient management was handled by the STI clinic. The STI clinic communicated the laboratory test results to the participants via routine STI clinic protocol. This entailed a text message in cases of a negative result and phone call in case of a positive result or when further contact was required. Participants were invited to attend the STI clinic when needed, such as for treatment, partner notification, counselling, and further diagnostics, when the self-taken sample was deemed inadequate. The role of the STI clinic was to oversee the implementation process and to manage all logistics and patient STI care.

Data collected for evaluation purposes

During the pilot implementation, HIV treatment providers provided coded and aggregated data on age and country of birth (aggregated for MSM who accepted a test kit and those who did not) and a frequency list of provider's reasons for not offering a sample kit and MSM's reasons for refusing an offered sample kit. Country of birth was categorized in western

(born in Europe, Northern America, Oceania, Japan or Indonesia, according to the definition of Statistics Netherlands (https:// www.cbs.nl/en-gb)) and non-western countries.

When MSM refused a sample kit, the healthcare provider asked for the reason (open-question). For feasibility and time reasons for the healthcare provider, the healthcare provider filled in the patients response on a prespecified list, with also an open-text response, if none of the pre-specified options were suitable. Due to privacy issues only aggregated data was available on reasons for declining for this study.

MSM who underwent HIV/STI testing provided quantitative data on their socio-demographics, STI testing history, risk behaviour, and experiences with the home sampling kit by completing the online questionnaire. The questionnaire was available in Dutch and English. The content of the online questionnaire was similar to the medical history form regularly obtained at STI clinic care, with the addition on questions on user experience of the home sampling kit (See Online Additional file 1 for a list of questions asked).

Further data collected included quantitative process data on test-kit use and return and STI diagnostic data. We also collected qualitative information (from our regular group meetings) regarding the users' experiences in the logistics (acceptability and feasibility) of the implementation process from all professionals involved. These included the healthcare providers of the HIV hospital clinic (offering STI kits), logistical team members (handling the sampling kits), laboratory staff (testing the samples), and care providers (nurses, doctors, assistants) of the STI clinic (providing patient care).

Sampling-kit content and laboratory testing

Each sampling kit contained an information package, with information about HIV/STI in general, and instructions on home sampling procedures and on how to return the samples. Kits included a swab for oral CT and NG, a swab for anorectal CT and NG, a urine collection tube for genital CT and NG and for syphilis and HBV testing, and a small blood collection tube with two finger prick sticks for capillary blood sampling. Sampling kits could be returned free of charge to the STI clinic of South Limburg via regular postal mail. Samples were tested in the medical microbiology laboratory at Maastricht University Medical Centre. Swabs and urine were processed with a polymerase chain reaction for CT and NG (Roche Cobas 4800, Roche Diagnostics, Basel, Switzerland). A syphilis screening test (*Elecsys® syphilis immunoassay*, Roche, Basel, Switzerland) was performed. However, when MSM

reported a history of syphilis in the standardised questionnaire, a rapid plasma reagin reditest (Biokit, Barcelona, Spain) was performed to measure the activity of the infection by antibody titre [16].

When MSM stated in the standardised questionnaire that they were HBV unvaccinated, HBV serology was performed on the blood sample. In case of a positive anti-hepatitis B core antigen test, hepatitis B surface antigen (HBsAg) test and anti-HBs (HBsAg II and anti-HBs II, Roche, Basel, Switzerland) were performed to determine HBV status.

Implementation evaluation

The quantitative evaluation included descriptive statistics to assess the proportions of [1] adoption by providers (i.e. HIV care providers offering sampling kits to their MSM patients and reasons for not offering a sampling kit, [2] participation (i.e. the sampling-kit acceptance by MSM and reasons for not accepting a sampling kit), and [3] other indicators such as the proportion of test kits returned, STI diagnosis, test history, and HBV vaccination. We reported the user experiences of MSM who underwent testing.

Furthermore, regarding the qualitative evaluation of user experiences, we described the barriers in the implementation process during the evaluation meetings with key professional stakeholders.

Results

Adoption (offering tests by care providers)

Of the 129 MSM who attended the HIV treatment clinic for HIV care (see Fig. 1), mean age was 46 years and 60.6% MSM had a western country of birth. 110/129 MSM (85.3%) were offered a home sampling kit. Reasons for not offering a sampling kit by providers were as follows: other medical priorities had to be considered (10/19, 52.6%), MSM did not understand the test instructions' language (Dutch or English) (5/19, 26.3%), MSM were recently tested for STI (3/19, 15.8%), MSM were not sexually active (1/19, 5.3%), or the care provider forgot to offer the sampling kit (1/19, 5.3%). The mean age of MSM who were offered a home sampling kit was 47 years, and 84.5% of MSM had a western country of birth (93/110) (Table 1).

Table 1. Demographic data on adoption, participation and return (aggregate level)

	Offered sampling kit			Accepted sampling kit			Returned sampling kit		
	n	mean age	Western country of birth (%)	n	mean age	Western country of birth (%)	n	mean age	Western country of birth (%)
Yes	110	47	84.5	64	46	87.5	29*	50**	89.3*
No	19	43	57.9	46	47	78.3	35	na	na

*One patient refused contact after returning sampling kit and was excluded in further analyses

** n=25, 1 MSM excluded, missing data in 3 MSM

na;not available; Demographic data from MSM who accepted a sampling kit, but did not return the sampling kit was not available due to medical ethical considerations.

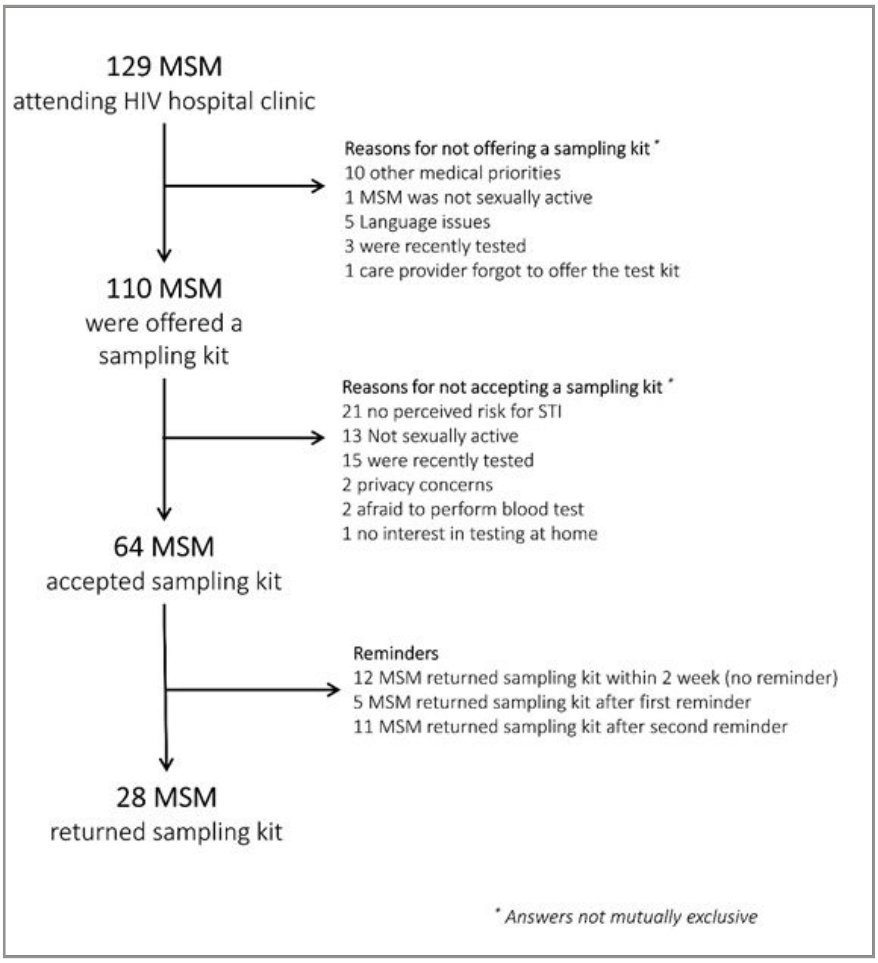

Figure 1. Flowchart of adoption, participation, and return of home sampling kits in a hospital setting (Human Immunodefiency Virus treatment centre)

Participation (accepting tests by men who have sex with men [MSM])

Of the 110 MSM who were offered a sampling kit, 64 (58.2%) accepted a sampling kit (Fig. 1). Reasons for not accepting a sampling kit were as follows: no perceived risk for STI (21/46, 45.7%), recently tested for STI at the STI or GP's clinic (15/46, 32.6%), or were not sexually active (13/46, 28.3%). The mean age of MSM who accepted a home sampling kit was 46 years, and 87.5% of the MSM had a western country of birth (56/64) (Table 1).

Return (sampling-kit return by MSM who accepted the home sampling kit)

A total of 29 out of the 64 (45.3%) MSM used and returned the sampling kit; one participant refused contact after returning the sampling kit and was subsequently excluded in further analyses. Moreover, 12 out of the 28 (42.9%) MSM returned their sampling kit within 2 weeks, without a text message reminder. The remaining MSM (n = 51) received a first text message reminder 2 weeks after receiving the sampling kit. Furthermore, 5 out of the 51 MSM returned their sampling kit within 2 weeks after the first reminder, and the remaining MSM (n = 46) received a second text message 2 weeks after the first reminder. Additionally, 11 out of the 46 MSM returned their sampling kit within 6 weeks. In total, 16 out of the 28 (57.1%) MSM returned their sampling kit after receiving a text reminder. The mean age of MSM who returned the sampling kits was 50 years (n = 25, missing data in 3 MSM) and 89.3% had a western country of birth (Table 1).

Test history, sample adequacy, and sexually transmitted infection (STI) diagnosis in testers

Of the 28 MSM who used a sampling kit, 10.7% (n = 3) were never tested before for STI (other than HIV) and 10 (35.7%) tested recently (in the past 3 months) (Table 2). Moreover, 64.3% (n = 18) of MSM were HBV vaccinated.

Table 2. Characteristics of the testers and their experiences with home sampling

	n (%)
Self-reported test history (N=28)	
Never tested for STI (other than HIV)	3 (10.7)
Tested for STI in the past 3 months	10 (35.7)
Tested for STI in the past 3-12 months	9 (32.1)
HBV vaccinated	18 (64.3)
STI diagnosed (N=28)	
Newly diagnosed STI (in home-care programme using home sampling)	5 (17.9)
Successful sampling and testing (N=28)	
Successful oral CT and NG testing	28 (100)
Successful genital CT and NG testing	28 (100)
Successful anorectal CT and NG testing	28 (100)
Blood sample >100 µl	23 (82.1)
Successful syphilis diagnosis (regular care)	17 (60.7)
Successful syphilis diagnosis (individual approach required)	5 (17.9)
Experience with home sampling (N=23)*	
Test instructions: (very) clear	22 (95.7)
Home sampling would be their test method of choice in the future	14 (60.9)
Would give a home sampling test to a peer (friend or sex partner)	17 (73.9)
Benefits of home sampling: testing when convenient and at own time	18 (64.3)
Benefits of home sampling: testing at home	13 (46.4)
Benefits of home sampling: no transportation required	13 (46.4)

*Missing questionnaire data from five individuals

All (100%) self-taken urine and swab materials were sufficient for further laboratory processing and testing. A total of 23 (82.1%) self-taken blood samples contained more than 100 µl of blood and thus were sufficient for HBV and syphilis screening, and these samples also had sufficient residual blood for HIV screening. However, 18 out of the 28 (64.3%) MSM reported a history of syphilis, requiring more sample materials for syphilis diagnostic work-up; 8 out of the 18 (44.4%) MSM had insufficient material and were further managed with tailored care (e.g. further tested at the STI clinic). All were negative for a new syphilis infection.

Using home-sampling in our programme, 5 out of the 28 (17.9%) MSM were newly diagnosed with one or more STI (i.e. genital CT, rectal CT, oral NG, rectal NG). All diagnosed MSM were asymptomatic treated and counselled at the STI clinic.

User experiences: MSM who underwent testing

The majority of MSM reported that the instructions provided in the sampling kit were clear. The main benefit of home sampling was the convenience in taking the samples (see Table 2). One MSM reported unclear blood sampling instructions. A number of MSM reported that home sampling (rather than sampling at clinic) would be their test method of choice in the future; MSM would not only recommend such sampling to a peer but also would provide a home-sampling kit to other peers themselves. Some MSM reported, to their HIV healthcare provider, that the online questionnaire was significantly extensive, and had concerns about their privacy.

User experiences: hospital providers

HIV care providers reported that overall, offering sampling kits was an easy and quick way to offer an STI test to a patient. However, offering sampling kits sometimes led to additional questions from patients during their regular HIV treatment centre visit (normal duration, 20 min), which was considered time consuming as it could take up HIV care providers' (nurses and physicians) additional 5 min' extra time. As an addition to a future programme, providers stated they would prefer the possibility of handing out the sampling kits to their patients' partners, by providing their patients with an extra sampling kit, as this was specifically requested by a few patients.

User experiences: STI clinic providers

STI clinic care providers reported that overall, home sampling kits could be a valuable addition to regular STI care for MSM related to costs and time; however, some components needed to be improved. STI clinic providers handled the logistics of the programme and STI patient care. Nurses handling the sampling kits felt it was time consuming when the sampling materials were insufficient or when the standardised questionnaire was incomplete as this required additional effort from the clinic nurse (e.g. when syphilis or HBV vaccination status was unknown). Physicians from the STI clinic acknowledged that syphilis diagnosis in MSM who had a history of syphilis can be complicated. First, a number of testers did not provide sufficient blood samples for a full diagnostic work-up; hence, a nurse communicated with the testers for an additional STI clinic visit. Second, even in the case of sufficient self-taken blood samples, the interpretation of the syphilis laboratory tests is difficult when no preceding syphilis test results are available for this patient. Thus, the STI clinic providers (after MSM consent) had to perform further actions such as searching the MSM's medical records, initiating phone calls to GP/HIV treatment specialist, and performing an additional

HIV/STI testing at the STI clinic. Hence, nurses suggested that obligatory questions should only be included as part of the data collection methodology so that missing necessary data will be avoided. Suggestions regarding effective patient management in case of a syphilis history were not reported because this has been also been encountered in routine face-to-face clinical practice.

Discussion

In this study, we performed a pilot implementation of a home-care programme to improve the HIV/STI care of MSM using home sampling kits combined with highquality sexual healthcare. In addition to previous studies, who assess and acknowledge the use of home sampling for bacterial STIs or HIV [12, 13, 17, 18], our home-care program includes bacterial STI, as well as HIV and syphilis testing, follow-up treatment and comprehensive sexual healthcare and can be sampled at home and send with postal mail for laboratory testing.

Here, the programme was pilot-implemented in the hospital HIV treatment setting to improve the uptake of STI testing and sexual healthcare in HIV-infected MSM. Our evaluation revealed that adoption of the programme by HIV care providers was adequate, that is, 85.3% of patients were offered a home sampling kit. Participation, that is, acceptance of sampling kits by MSM, was 58.2%, and sampling kit return was 43.8%. Samples that were self-collected were generally adequate, but establishing a syphilis diagnosis was complex in case a patient reported a history of syphilis. Several barriers at the logistic and the care provider level were reported, suggesting that further optimisation of our home-care programme for MSM with comprehensive sexual healthcare is required.

In developing the programme and during its implementation, regular meetings and in-person contact were established between the care providers (implementers) and the programme developers, which is considered essential to sustain and promote the use of the programme. We involved key stakeholders and implementers already in the early development phase of the programme to tailor the needs of care providers, share knowledge, create trust, and work on a shared goal for the project [19]. With these steps, we enhanced the implementation behaviour [future reference].

Our implementation pilot aimed to test the logistics of the programme components, to assess acceptance and feasibility and user experiences, and to determine the barriers of the programme.

The programme was established using home sampling methods, which are considered important in increasing the test uptake. Our pilot implementation confirmed that the use of text message reminders was important to increase the sampling-kit return [20, 21].

MSM involved in the programme reported a positive attitude towards home sampling. Previous studies have also shown that self-sampling increases CT and NG testing in patients undergoing HIV/STI testing in HIV clinics [22]. Besides urine samples and anorectal and oropharyngeal swabs, the test kit included a blood sample to test for syphilis and HBV. Our study confirmed that most MSM considered finger prick blood sampling feasible and acceptable based on the previous studies [23, 24].

Home sampling kit collecting blood (allowing for syphilis, HBV, and HIV screening) samples is a unique addition to home sampling kits for chlamydia and gonorrhoea. Nevertheless, in HIV-positive patients, establishing the diagnosis of syphilis was difficult, and a suboptimal diagnosis can only be established when a single self-collected blood sample is used.

The proportion of MSM with previous syphilis infection was high (18/28, 64.3%) [25], and in these patients, a syphilis screening test (requiring a small amount of blood sample) is not required. However, self-taken blood sample was insufficient for a full syphilis work-up and diagnosis in 44.4% of the patients who had a history of syphilis (8/18). Hence, additional efforts (e.g. initiating phone calls to the involved patients, obtaining patients' consent when searching their medical history, or additional blood drawing at the STI clinic) are required. Discussing these issues with the project team, the addition of a second self-taken blood tube in the sampling kit to obtain sufficient blood samples was not considered patient-friendly and hence not a desired solution. In a previous study, dried blood spot was used for syphilis screening [23]. However, this method was also not optimal as not all samples were adequately obtained. Hence, additional efforts (searching the patients' medical history) are still required. Although development and implementation for syphilis home sampling is promising [23, 26, 27], it is also challenging. A large study from the UK with home sampling using capillary blood sampling found that only 54% of the samples contained sufficient blood for syphilis testing [28]. Although in our study, we had more samples (82.1%) that contained

sufficient blood for testing, lack of knowledge on patient syphilis history made syphilis diagnosis difficult in this particular approach taken.

In MSM with a lower proportion of past syphilis, such as HIV-negative or unaware patients, a syphilis screening test is usually considered the test of choice. An additional non-blood (saliva) HIV screening tests to the test kit may be considered but may not be required as in our study 82.1% (23/28) would have had sufficient blood samples for both syphilis and HIV screening.

Despite the difficulty in diagnosing syphilis, the programme can be a valuable extension to public health and regular care to reach MSM who do otherwise not receive comprehensive and regular sexual healthcare.

Because of the provider's and the MSM's significant effort, a comprehensive STI diagnosis was achieved (including syphilis) for all patients. However, the following question remains: Will the complexity of syphilis diagnosis negatively affect the home-care programme's effectiveness? Based on our evaluation meetings, when discussing these issues, the benefits of home-care programme for public health (reaching more untested MSM) and individual patient management (providing a valid test result immediately) created a significant tension between stakeholders. Hence, properly weighting the benefits of the homecare programme for public health and individual patient care is important. Cost-effectiveness studies may shed further light on this issue. Adding STI screening to regular care at HIV treatment centres can be cost-effective in the Netherlands [29].

We encouraged MSM to return their sampling kit by message reminders, which increased the return rate from 18.8% (12/64) to 43.8% (28/64). Other studies showed higher HIV/STI home sampling return rates (55–84.5%) [30–32]. In our study, more than half of the distributed sample kits were lost. The sampling-kit return rate could possibly be increased if MSM were initially required to perform several actions in order for them to receive the kit, for example, by initially committing themselves to complete the forms online, read the information about home sampling, and exert some effort in completing their online medical history before receiving a sample kit [30]. Another way to increase the sampling-kit return rate could be by using other distribution methods, for example, peer dissemination [33]. The effect of different distribution methods among MSM on sampling-kit return rate should be further explored.

This study has some limitations. First is the generalisability of results. This pilot study was conducted in HIV-positive MSM who were already enrolled in HIV care. Use and acceptability of the sampling kits could be different among the general MSM population, such as the use of syphilis testing considering that HIV-positive MSM with the highest proportion of previous syphilis underwent HIV/STI testing in this study. Second is the limited number of MSM included in this pilot implementation study. Considering the objectives of our study, the number of MSM who participated in the study was insufficient for further data analysis. Nevertheless, information from 25 MSM was valuable to give an insight in user experiences to home sampling. Implementing this programme in a larger group (e.g. HIV-negative MSM or MSM who are not enrolled in care) would provide more insight on the generalisability of results to the broader MSM population. Third is related to medical ethical considerations considering that the demographic information of MSM who did not participate in the study is not available. This information would give better insight in characteristics of those who did not accept or did not return a sampling kit and could be used to inform future work. More research is needed to assess reasons for not returning sampling kits to improve return rate in future home-sampling sexual healthcare. Our study group will assess if applying for a sampling kit online and subsequent sending reminders after receiving a sampling kit will increase return rate in a new implementation of the programme 'Limburg4- zero', to reach the broader population of MSM.

Conclusion

The home sampling programme increased STI test uptake and was considered acceptable and feasible for most MSM and their care providers and could be a valuable extension to current sexual healthcare. In an HIV-positive population, syphilis diagnosis may be challenging when only single self-taken blood sample is used. From a public health view, the home-care programme is promising to deliver comprehensive STI care in the home setting for MSM. Results from this pilot study could be used to optimise and implement home sampling for HIV/STI tests in the future.

Supplementary Information

The online version contains supplementary material available at https://doi. org/10.1186/s12879-020-05658-4.

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CHAPTER 7

General discussion

In this thesis we discussed public sexual health care strategies targeted at two components of the reproductive rate model of infectious diseases in relation to HIV/STI. We explored possible hidden *Chlamydia Trachomatis (CT)* reservoirs, to address the **probability of transmission**, and we studied HIV/STI testing behaviour and improvement options among MSM as part of reduction strategy of the **duration of infectiousness**.

Decrease probability of transmission per contact: hidden reservoirs

Anorectal CT

We attempted to clarify a possible mode of transmission in rectal CT. Over half of rectal CT cases in MSM and in women are observed without reported anal sex [1, 2]. A growing body of evidence suggest that rectal exposures other than unprotected anorectal sex may infect the anorectal site with CT [3]. Data from the Australian Health in Men (HIM) study, a large longitudinal cohort study among 1,400 MSM, found that receptive rimming (anal licking) was an independent risk factor for rectal CT [4]. Furthermore, oropharyngeal CT is hypothesized to play a role in anorectal CT, as a form of autoinoculation within the same person [5]. Researchers pose that oropharyngeal CT infections may lead to anorectal infection via the gastrointestinal tract, which is referred to as the GI tract hypothesis [5, 6]. So far, the evidence on this possible route is inconclusive.

GI tract hypothesis

In the past years, animal studies have been reported to provide insight and evidence regarding the GI tract hypothesis. In mice, results have been presented in favour of the hypothesis that oropharyngeal CT could lead to anorectal CT via the GI tract. Studies suggest that the immune response of the GI tract is down-regulated, which may facilitate Chlamydia muridarum (CM) to survive and replicate in the GI tract indefinitely [7]. One study also suggest that the GI tract of mouse may have a differential susceptibility of chlamydiae to azithromycin than the genital tract, which could possibly reflect failure of antibiotic treatment for the GI tract [8]. However, because research is done in mice, and with CM instead of CT it is uncertain whether these results also apply to humans.

Although it is suggested that CT can survive the acid environment of the stomach in humans [9, 10], the biologic plausibility of CT transmission from the mouth to the rectum of the same person remains uncertain. Bavoil et al (2017) hypothesize that active oral sex can introduce CT to the GI tract [11]. They suggested that these detections are often missed by healthcare

providers when only cervical CT testing is performed and missed by patients because of the lack a of immune response of the body to CT bacteria [11].
Borel et al (2018), detected chlamydial DNA in the appendix and colon of patients with a history of chlamydia [12]. No chlamydial DNA was found in patients without a history of chlamydia. However, as these DNA detections were done by NAAT tests, it was not possible to indicate whether the detected DNA represented viable bacteria that were able to replicate and infect [12]. As this DNA was found in close proximity of the rectal site, it could be debated that these bacteria originated from the rectum, rather from the oropharyngeal site. Chlamydial inoculation from the genital tract to the GI tract has been shown in mice [13].

This thesis

In **chapter 2** and **chapter 3** we explored the role of oral (sexual exposure to) CT in rectal CT in an epidemiological analyses by evaluating a possible relation between oropharyngeal CT and subsequent anorectal CT infection. In this large longitudinal study we did not observe a risk from preceding (up to 24 months) oropharyngeal CT for subsequent anorectal CT infection after correction for confounding factors. A possible minor association with a potential impact on a limited number of individual patients cannot be ruled out, as we used an epidemiological design rather than a human experiment.

Recommendations

More clinical or epidemiological studies with human data are needed in order to confirm or dismiss the GI tract hypothesis. For example with data on routine testing for oropharyngeal, anorectal and genital CT and data on the genotypes of the bacteria. With genotyping, specific genotypes types can be distinguished which could give a better understanding of transmission between and within people. However, genotyping has also limitations, as same genotypes found on different anatomic locations can also be a result of infections from the same a partner, instead of autoinoculation. In the case we had found evidence for the oral-anal route in MSM, current public health care policy in the Netherlands would be sufficient to detect and treat anorectal CT infections, as extragenital screening for MSM is already suggested as best practice in Dutch STI clinic guidelines. However, its urge to comply to these guidelines would be even more relevant. Furthermore, GPs and HIV treatment centres in the Netherlands do currently not have as extensive testing guidelines and only include extragenital CT testing after reporting symptoms or anorectal sex. In the case we had found evidence

for the oral-anal route in women, current screening guidelines should be considered, as they currently not recommend routine screening on oropharyngeal and anorectal locations. However, screening and treatment of asymptomatic anorectal and oropharyngeal infections is under debate as there is limited evidence about the individual clinical benefits associated with treatment of these infections [14, 15]. From a public health view these infections should be treated, as it is suggested that these infections may facilitate disease spread when left untreated [14, 16].

At the population level, mathematical modelling studies posed that oropharyngeal CT does not play a major role in CT transmission in MSM [17]. Results from our epidemiological study, i.e. the absence of effect, and the current literature examining the GI tract hypothesis do not initiate a recommendation to change current HIV/STI testing and care policy.
Nevertheless, oropharyngeal testing in MSM is still relevant for other reasons. Oropharyngeal *Neisseria gonorrhoeae* (NG) can play a major role in ongoing NG transmission [18, 19]. More than half of oropharyngeal NG infections occur without genital or rectal infections and thus would not coincidentally be treated if not tested for [20]. Extragenital CT testing and extragenital NG testing (at the rectal, oral, and genital site) for MSM is already recommended in international guidelines and implemented by Dutch STI clinic in practice [21]. For GP and the hospital setting, such as HIV treatment centers, extragenital STI testing is not always part of routine HIV/STI screening in MSM and care and thus could be improved.

Decrease duration of infectiousness: testing and treatment

In the past decade, numerous initiatives have been developed, implemented and sustained in order to reduce HIV/STI among MSM. In this thesis we focused on testing, as testing is a key prevention strategy and a main entry point into care [22]. Worldwide, self-testing (i.e. where the patients can read the results) is accepted by MSM, especially due to the convenience and private nature of self-testing [23, 24]. For HIV, self-testing is recommended by the world health organization (WHO) as an additional HIV testing approach, as these test are reliable and associated with increased uptake and frequency of testing for HIV [25, 26]. Self-testing for HIV has been shown to be as accurate as healthcare professional testing [27]. For bacterial STIs, such as CT and NG, self-testing has not yet been proven reliable due to unreliable tests. However, self-collection of samples (self-sampling), where the patients sends self-collected samples for laboratory testing, was found to perform as well as or better than clinician-collection for STI detection [28].

Although many scientific studies assessed the use, acceptability and reliability of self-sampling tests for HIV/STIs, it is not (free-of-charge) available in every country yet. A reason for the delayed adoption of home-sampling includes that not all HIV/STI care services are currently equipped for care in the home setting, due to lack of funding, infrastructure or knowledge. Furthermore, the introduction of self-testing and self-sampling, brings new challenges for HIV/STI care, including no or nonstandard counselling following receipt of test results, and difficulty in providing linkage to care. Concerns from healthcare professionals rise about its effects on the well-being of MSM due to lack of counselling and follow-up opportunities [29]. A treatment consultation is intended to have risk-reducing impact on sexual risk behaviour. However, is has been shown that not only counselling, but also a testing itself or a positive test results leads to behaviour change [30]. After testing, irrespective of the test results, visitors of public health service reported increased intentions toward condom use and STI testing, and decreased shame after testing [30].

Although self-testing or self-sampling is not implemented in regular care, it is now more important than ever, in light of disruptions to routine care resulting from COVID-19 control measures. Care-at-home has become even more urgent and needed, as sexual healthcare facilities are closed or have a lower accessibility. COVID-19 increased the urgency of distance care and its relevance and importance is acknowledged on worldwide and country policy level. Healthcare professionals also acknowledge the relevance of care at home. However, whether this will lead to actual increase of sexual healthcare at home, such as through home-sampling tests, has yet to been seen.

This thesis

As the benefits of using home-sampling kits, and its ability to reach MSM with HIV/STI care have been well-described, we wanted to introduce home-sampling to extend our efforts in current STI care for MSM. To do so, we developed a home-care program which provides testing, treatment and counselling for MSM and an intervention to stimulate testing behaviour among MSM in the Netherlands who currently do not get (regularly) tested for HIV/STI.

Who should we target

To optimize sexual healthcare for MSM, available resources need to be distributed to target those who are at highest risk for HIV/STI. For improving HIV/STI testing, it should be first

explored which factors contribute to testing behaviour. As factors for (not) testing vary across countries, populations and culture it is valuable to understand and explore the population in which sexual healthcare will be implemented in order to know who should be targeted and which methods will be effective.

Living in areas with different urbanisation levesl are related to sociodemographic factors, which have shown to be an important proxy for healthcare engagement. Differences in urbanisation level introduces different barriers and opportunities for healthcare. Rural-urban differences exist in health concerns and barriers to access [31].

Highly urbanized areas, such as cities and municipalities, account for a significant percentage of the global HIV burden. Cities and municipalities face many challenges in their urban HIV responses, include overcrowding, homelessness, population migration and high rates of other communicable diseases [32]. Vulnerability to HIV is higher in urban centres compared with rural areas. Therefore, the Fast-Track Cities initiative (*www.fast-trackcities.org*) was lounged in 2014, a global partnership with a commitments to reach shared objectives to getting towards zero new HIV infections and zero AIDS-related deaths.
Although global collaborations and strategies are important to move towards zero HIV infections, local and regional adaption is an essential addition to reach the last proportion of people who are unaware of their HIV status and those not in HIV-care. To identify the most effective regional approaches to improve testing, the local situation (e.g. HIV testing frequency and barriers towards HIV testing) need to be explored.

In **chapter 4** we describe HIV testing behaviour of MSM living in highly (>2,500 living addresses/km^2) and non-highly (≤2,500 living addresses/km^2) urbanized areas in the Netherlands. We found that HIV testing proportions and factors associated with never testing and not recent testing were found to differ between MSM in highly and non-highly urbanized areas of the Netherlands. The proportion never tested is especially high (25.2%) in MSM living in non-highly urbanized areas. In non-highly urbanized areas, but not in highly-urbanized areas, a high HIV severity perception, low HIV risk perception, and reporting having a low share of gay people among friends was associated wit not recent or never HIV testing. Therefore, HIV-testing strategies should be targeted to reach MSM in different urbanization-settings, adapted to local barriers and preferences and incorporated these associated factors.

Development of healthcare innovations

Exactly how and when to use evidence, theory, and community-based participation during development remains a challenge when addressing innovation in healthcare [33]. Thus, a theory-based approach and documentation of the development process of a new care-approach (intervention) is often lacking in the development of a novel healthcare program. Documentation of development is important for transparency of the creation of healthcare programs and innovations and lessons learned from the development could benefit other healthcare professionals who are developing healthcare programs. In **chapter 5** we used intervention mapping (IM), a well-described method based on theory for development of healthcare interventions, to develop an intervention to stimulate behavior change of MSM to get themselves tested for HIV/STI [34].

As the Dutch healthcare system is characterised by distributed decision-making, there are generally many stakeholders involved in the implementation of innovations in healthcare practice [35]. Regular meetings and in-person contact between healthcare providers (implementers) and program developers is considered essential to sustain and promote the use of the program. In our study we involved key stakeholders and implementers already in the early phase of intervention development to tailor the needs of care providers, share knowledge, create trust, and work on a shared goal for the project [36]. This also created a solid base for collaboration between different care providers. The role of linkage and exchange through stakeholders and organizational managers create important networks for translating scientific and practical knowledge into action [37].

Implementation

After careful and though-out development of a healthcare intervention or innovation, implementation needs to be prepared. Implementation usually is not an easy tasks and should be carefully planned and carefully evaluated. Important factors for implementation success include realistic timescales for the changes and the involvement of organisation managers of the implementers [38]. Involving organisation managers from all levels is important in planning for sustainability, and they need to acknowledge the need to target this group specifically with development activities and support [38].

Determinants of successful implementation can be attributed to the innovation itself, the target group of executers and users of the innovation, the social and practice setting, the organizational system, regulation and economic structures and the strategy for dissemina-

tion and implementation [39]. Structural conditions, such as financial and facilitative recourses should be sufficient for the implementation to succeed [40]. These factors also determine the possibilities and choices for implementation strategies. Environmental factors have also an influence on the effect of implementation, such as support of supervisors and coworkers, sufficient capacity and time of the target group who should implement the innovation. When implementing an intervention with knowledge gained from previous studies, adjustments of the knowledge to local circumstances is needed and is part of the implementation. Even if a particular intervention has proved effective, it needs to be adapted to the local situation when implemented elsewhere [41]. Therefore, it is essential to explore and map the local situation in which an intervention is implemented and work together with stakeholders who will be the implementers, as they have knowledge on the current local situation.

To reveal factors for successful implementation of our developed home-care program, discovered implementation hurdles and share lessons learned, we described in **chapter 6** our findings. We pilot tested the implementation of the novel developed home-care program for MSM in the hospital setting (HIV treatment centre) among HIV-positive MSM. Evaluation from the pilot implementation revealed several barriers and challenges. Especially towards counseling opportunities and syphilis diagnosis. In our pilot population, e.g. HIV-positive MSM, 64.3% had a previous syphilis infection. This makes a screening test not necessary, but a full syphilis diagnosis needed to be done. This required MSM to come to the clinic for additional blood drawing and searching their medical history. Currently, our research group is exploring innovative diagnostics to be able to test for syphilis and solve this issue.
During implementation different stakeholders have different priorities, such as individual patient outcome or public health outcome. From a public health view it is acceptable that not all MSM are reached with this care, and that some MSM have to come to the clinic for a follow-up diagnosis. From an individual patient approach, every patient need to be tested for all relevant STIs and need to receive a test result and counselling. This created tension between stakeholders. Public health gain and the individual patient health needs to be balanced and both be sufficient. This highlights the skills needed for the role of the program and implementation plan developers and executers, as they constantly needs to liaise between different interest groups in the implementation process.

Recommendations towards implementing HIV/STI home-sampling

MSM: Although home-sampling is adequate for screening for syphilis, a full diagnostic for those with a history of syphilis is not recommended at this time, with the currently used methods. Innovative options are being explored at the moment. To improve efficiency of home-sampling it is advised to gather information on medical history on HIV, HBV and syphilis and triage beforehand on those who need a screening tests. For those who need a more extensive blood research, combined with anamneses on syphilis or HIV history, or would benefit from speaking to a sexual health professional, an invitation to the clinic would be better suitable. Thereby, a home-sampling opportunity can serve as a low threshold entry point to care. Based on findings in this thesis we conclude that HIV/STI home-sampling is a beneficial addition to current sexual health care for MSM, although it may not be suitable for all MSM and a targeted approach remains needed.

Healthcare providers: HIV/STI Home-sampling for MSM can have the potential to unburden health care providers. However, implementation of innovations, which may require different or new work procedures, can bring challenges. Therefore an implementation plan for healthcare providers and a pilot implementation is advised before implementing an healthcare intervention or innovation. This can reveal and remove barriers for healthcare providers towards new work procedures and improve sustained use of the program after implementation. Also, involving (a representative of) implementers in the development process will increase knowledge sharing, create a care-network and increase the likelihood of sustained use of the program after implementation.

Currently, our research group is further developing this home-sampling care program for MSM called 'Limburg4zero'. The barriers found in our studies will be assessed and improved and this program will be implemented in a broader population of MSM.

Overall conclusion

The results of this thesis contribute to understanding HIV and STI transmission among MSM.

The studies included in this thesis contributes to understanding transmission and improving and optimizing HIV/STI care in men who have sex with men (MSM). In our study, we found no evidence for the oral-anal CT hypothesis, therefore, based on our results no adaptions in current healthcare are advised. However, more research need to be done to confirm our results.

We developed and implemented a home-care program using self-sampling for HIV/STI for MSM. In the development we involved stakeholders and experts for behaviour change. In the pilot implementation we encountered issues with syphilis diagnosis, return rate and different interest from different stakeholders. Currently, we are further developing this home-care program where we address and improve these issues and make this program available for a broader MSM population.

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CHAPTER 8

Summary
Nederlandse samenvatting
Impact paragraph
Portfolio
Dankwoord

SUMMARY

The studies included in this thesis contribute to understanding, improving and optimizing HIV/STI care in men who have sex with men (MSM). We explored challenges in reaching MSM for providing recommended testing and care and sought for possible solutions to optimise this. In this thesis two components of infection transmission control are discussed in relation to HIV/STI care optimization in MSM: decreasing probability of transmission per contact by addressing hidden infection reservoirs and decreasing the duration of infectiousness by addressing timely treatment and testing.

Chapter 1 provides a general introduction on transmission and prevention of HIV/STI among MSM. MSM are a group at increased risk for HIV and other STIs like *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG), hepatitis B (HBV) and syphilis.
There is an on-going debate on whether oropharyngeal CT infections can inoculate the human gastrointestinal tract, and subsequently lead to anorectal CT infections. It is yet unclear whether the human gastrointestinal tract can host CT bacteria and whether the anorectal site can be infected via the oral-intestine-anal route. **Chapter 2** explores this possible transmission route by assessing the relation between preceding oropharyngeal CT and subsequent anorectal CT with an epidemiological approach on longitudinal patient clinic-registry data between 2009 and 2016 from MSM (n=17,125) and women (n=4,120) from two Dutch STI clinics. When adjusting for confounding factors, previous (from 3 weeks up to 24 months) oropharyngeal CT was not a risk factor for subsequent anorectal CT in MSM (OR 1.33; 95%CI 0.86-2.07; P=0.204). The role of the gastrointestinal tract cannot be excluded with this epidemiological study, but the impact of preceding oropharyngeal CT on anorectal CT infection is likely limited. In **chapter 3**, we advised other researchers to take caution in overinterpreting relations regarding the oropharyngeal-anorectal hypothesis. With cross sectional data of anorectal CT infections, reported cunnilingus and receptive anal behaviours it is hard to prove causal relations and a possible role of the GI tract.

Chapter 4 describes HIV testing behaviour of MSM living in differently urbanized areas in the Netherlands. Between February and June 2018, the online survey 'Men & Sexuality' (SMS) was done in the Netherlands. The study population for analysis contained 3,815 MSM. When comparing proportions of MSM living in a high urbanized area versus MSM living in a non-high urbanized area, 68.4% versus 54.9% of all MSM were recently tested, 19.8%

versus 19.6% of all MSM were not recently tested, and 11.8% versus 25.2% of all MSM were never tested. The main (47.4%) reason for never testing was a lack of perceived risk for HIV. The proportion never tested is especially high in MSM in non-urban areas. While sexual risk is associated with HIV testing regardless of geography, social environment does play an important role for HIV testing for MSM non-high urbanized areas, but not for MSM living in a high urbanized area. Social environment of MSM should be taken into account when designing interventions or healthcare innovations to reach MSM with HIV testing, especially in non-high urbanized areas.

Chapter 5 describes the systematic development of an intervention to stimulate MSM to get tested for HIV/STI, according to the intervention mapping (IM) approach. IM is a systematic six-step approach, which promotes evidence-based decision-making and involves stakeholders in the development of an intervention. The developed intervention was part of a broader regional home-care program, combining home-sampling for HIV, hepatitis B, syphilis, and extra(genital) chlamydia and gonorrhea, with counselling, treatment, and sexual healthcare.

In **chapter 6** we describe a pilot implementation of the home-care program in the hospital setting. Healthcare providers from the HIV treatment centre (Maastricht) were invited to offer free STI sampling kits for hepatitis B, syphilis, and (extra)genital chlamydia and gonorrhea to their HIV-positive MSM patients. Adoption of healthcare providers was 85.3% (110/129), participation was 58.2% (64/110), and sampling-kit return was 43.8% (28/64). Of the tested MSM, 82.1% (23/28) did not recently undergo an STI test (<3 months) and 17.9% (5/28) were diagnosed with an STI using a sampling kit. The home-sampling program increased STI test uptake and was acceptable and feasible for MSM and their care providers. Although text message reminders improver return of sampling kits, return could be further improved. Syphilis diagnosis was difficult with sampling kits in patients with a reported history of syphilis.

In **chapter 7**, all studies were discussed in a general discussion with concluding remarks and future directions for research.

NEDERLANDSE SAMENVATTING

De studies in dit proefschrift dragen bij aan het in kaart brengen van de transmissie van seksueel overdraagbare aandoeningen (soa's) en het verbeteren en optimaliseren van de HIV/SOA-zorg voor mannen die seks hebben met mannen (MSM). Uitdagingen en barrières worden beschreven om MSM te bereiken met goede seksuele gezondheidszorg en HIV/SOA testen. Daarnaast worden mogelijke oplossingen voor de barrières beschreven. In dit proefschrift worden twee onderdelen van infectieziektebestrijding behandeld in relatie tot de optimalisatie van de HIV/SOA-zorg bij MSM: het verminderen van de kans op overdracht per contact door verborgen reservoirs en het verkorten van de infectieduur.

Hoofdstuk 1 geeft een algemene inleiding over de overdracht en preventie van HIV/STI onder MSM. MSM is een groep met een verhoogd risico op HIV en andere soa's zoals *Chlamydia trachomatis* (CT*), Neisseria gonorrhoeae* (NG), hepatitis B (HBV) en syfilis.
Een wetenschappelijke discussie wordt gevoerd over de vraag of orale CT-infecties het menselijk maag-darmkanaal kunnen overleven en vervolgens kunnen leiden tot anorectale CT-infecties. Het is nog onbekend of CT-bacteriën zich in het menselijk maag-darmkanaal kunnen vestigen en of anorectale infecties kunnen ontstaan vanuit orale infecties via de gastro-intestinale route.

In **hoofdstuk 2** wordt deze mogelijke transmissieroute onderzocht door de relatie te beoordelen tussen de voorafgaande orale CT-infecties en de daaropvolgende anorectale CT-infecties. Hiervoor is gebruik gemaakt van longitudinale data van patiëntenregistratiegegevens tussen 2009 en 2016 van MSM (n=17.125) en vrouwen (n=4.120) van twee Nederlandse soa-klinieken. Na correctie voor confounders was voorafgaande orale CT-infectie (van 3 weken tot 24 maanden) geen risicofactor voor latere anorectale CT-infectie bij MSM (OR 1,33; 95%CI 0,86-2,07; P=0,204). De rol van het maag-darmkanaal bij anorectale infecties kan met deze epidemiologische studie niet worden uitgesloten, maar het effect van de voorafgaande orale CT-infecties op de anorectale CT-besmetting is waarschijnlijk beperkt.

In **hoofdstuk 3** worden andere onderzoekers geadviseerd om voorzichtig te zijn met het trekken van conclusies en interpretatie van data in relatie tot deze oraal-anorectale hypothese. Met dwarsdoorsnede data van anorectale CT-infecties en zelf-gerapporteerde orale en anale seks, is het moeilijk om causale verbanden en de mogelijke rol van het maagdarmkanaal aan te tonen.

Hoofdstuk 4 beschrijft het HIV-testgedrag van MSM die in gebieden in Nederland wonen met een verschillende urbanisatiegraad. Tussen februari en juni 2018 is in Nederland de online enquête 'Mannen & Seksualiteit' gehouden. De geanalyseerde onderzoekspopulatie in de studie in dit proefschrift bevatte 3.815 MSM. Bij het vergelijken van de verhoudingen tussen MSM die in sterk verstedelijkte gebieden wonen en MSM die in niet verstedelijkte gebieden wonen, is 68,4% versus 54,9% van alle MSM recentelijk getest. Van alle MSM zijn 19,8% versus 19,6% niet recent getest en 11,8% versus 25,2% van alle MSM zijn nooit getest. De meest voorkomende (47,4%) reden om zich nooit te laten testen was een lage risico perceptie op HIV. Het aandeel MSM dat nooit voor HIV getest is, is vooral hoog in MSM in niet-stedelijke gebieden. Hoewel seksueel risico geassocieerd wordt met hiv-testen ongeacht de geografie, speelt de sociale omgeving een belangrijke rol bij hiv-testen voor MSM in niet-stedelijke gebieden, maar niet voor MSM die in een hoog stedelijk gebied wonen. De sociale omgeving van MSM verdient wellicht meer aandacht bij de uitvoering van HIV testen in niet-stedelijke gebieden en kan dienen als aanknopingspunt bij het bereiken van de doelgroep.

Hoofdstuk 5 beschrijft de systematische ontwikkeling van een interventie om MSM te motiveren zich te laten testen op soa en HIV, volgens de *Intervention Mapping* methode. Dit is een systematische aanpak, die besluitvorming op basis van wetenschappelijke kennis en bewijs bevordert en belanghebbenden bij de ontwikkeling van een interventie betrekt. De interventie heeft als doel MSM te bereiken en te stimuleren om zich te laten testen voor HIV en SOA. De ontwikkelde interventie maakte deel uit van een breder regionaal thuiszorgprogramma, waarbij zelf afname voor HIV, hepatitis B, syfilis en (extra)genitale chlamydia en gonorroe werd gecombineerd met counseling, behandeling en seksuele gezondheidszorg.

In **hoofdstuk 6** wordt een pilot-implementatie van het thuiszorgprogramma in de ziekenhuisomgeving beschreven. Zorgverleners van het hiv-behandelcentrum (Maastricht) werden gevraagd om hun hiv-positieve MSM-patiënten gratis een zelfafname testpakket voor soa aan te bieden. De adoptie van zorgverleners was 85,3% (110/129), de deelname van

MSM was 58,2% (64/110) en het rendement van de testpakket was 43,8% (28/64). Van alle geteste MSM (n=28) had 82,1% niet recent (<3 maanden) getest op soa en 17,9% werd gediagnosticeerd met één of meerdere soa. Het thuiszorgprogramma verhoogde het soa-testgebruik en was aanvaardbaar en haalbaar voor MSM en hun zorgverleners. Het sturen van herinneringen per SMS zorgde dat meer MSM het testpakket retourneerde. Het diagnosticeren van syfilis was moeilijk met de zelfafname testpakketten bij patiënten met een eerder doorgemaakte syfilis infectie.

In **hoofdstuk 7** worden alle studies besproken in een algemene discussie met conclusies en aanbevelingen voor toekomstig onderzoek.

IMPACT PARAGRAPH

Research

Main objective and results

The main objective of this thesis to optimize HIV and STI care for men who have sex with men (MSM). In this thesis, we explored barriers and possible solutions for MSM who are not tested for HIV/STI on a regular base. Our mission is to use the available resources, such as time and money, for sexual healthcare in the most effective way to reach as many MSM as possible and move towards zero new HIV infections and reduction in new STI. Targeted care, fit to the individual needs, combined with self-sampling for HIV/STI can be key factors to reach the people who are currently unaware of their HIV status and thereby reducing the spread of HIV. We developed and implemented a home-care program using self-sampling for HIV/STI for MSM.

Scientific impact

Documentation of developments

In current literature and research, there is a lack of development-processes documentation and of best- and worse-practices for interventions to promote HIV/STI testing. Description of the development and implementation process can be useful for those willing to improve or change current healthcare with implementation of an innovation or a change of current practice. Our description can serve as a guideline for the development and implementation and lessons learned in this thesis can be used to improve other innovation projects.

Therefore, to share such insights, we described in our study the use of intervention mapping to design an intervention to promote self-sampling tests for HIV/STIs and enhance sexual healthcare among MSM. The systematic process and the clear documentation of the development process and pilot testing of our novel home-care program could be very useful to other public health professionals, from STI clinics, HIV hospital clinics, and general practitioner (GP) offices, who are developing healthcare programs. These results will also be valuable to public health professionals who want to use or implement home self-sampling tests for HIV/STI or other diseases.

New insights on oropharyngeal and anorectal CT infections come from the *FemCure* study and the currently ongoing *CHLAMOUR* study both in women, but with results that may also be applicable for MSM. The FemCure study demonstrated that spontaneous clearance of oropharyngeal CT is common; of those who did not clear CT, three-quarters had non-viable CT. This finding contributes to the debate on whether the oropharyngeal site should be considered important in CT control efforts. In contrast to what is found in oropharyngeal CT, anorectal CT based on self-taken swabs, as in routine care, frequently presents with viable CT. The *CHLAMOUR* study from our research group will provide insight in the viability of CT at different anatomic locations i.e. the anatomic sites samples by self-collection and the anatomic sites more upward in the body, providing some leads for the validity of self-collection when aiming to detect viable CT.

Social impact

Improved HIV/STI testing for MSM

Men who have sex with men (MSM) are at increased risk of acquiring HIV infections. Despite the presence of several public health and clinical efforts to increase the testing uptake, a number of MSM still remain untested; therefore, several infections remain untreated. To develop and targeted care, it is necessary to explore and understand associated factors with HIV testing behaviour. In this thesis we assessed this at different levels of urbanization in the Netherlands, as urbanization level is known to play a role in healthcare access and healthcare seeking behaviour.

Furthermore, fast testing can lower the burden of disease for infectious diseases. People with later stage HIV infections have a higher risk of progressing to AIDS or death, and have higher direct medical treatment expenditures. Improved testing could be effective in interrupting the transmission-chain, leading to reductions in HIV-incidence. Increased and early testing and treatment will eventually decrease the prevalence of HIV/STI and HIV/STI-related morbidity and mortality among MSM. The studies in this thesis demonstrate the usefulness of self-sampling at home and the importance of gaining insight into the possibilities of home-sampling as addition to regular sexual healthcare.

Care-at-home

With the current ongoing COVID-19 pandemic, care at distance combined with using eHealth technologies is important. Health services globally are struggling to manage the impact of COVID-19. Particularly in light of Covid-19 related disruptions to location-based care, developing and evaluating alternative models of care delivery is important, especially care that can be delivered in the home-setting. Regular public health sexual healthcare which can be provided at distance is an addition to clinic-based regular sexual healthcare. This includes eHealth and home-sampling for HIV/STI tests. This is an effective method to reach important target populations with care and tests. In this thesis development and implementation of such a home-care program is described. Home-sampling tests and care for HIV/STI complies with the needs of the target group, especially those living in less urbanized areas. Furthermore, it has the opportunity to offer care customized in the most effective way. For example, only offering full counselling to those who are in need of face-to-face counselling and offering others a less extensive, but suitable care-traject with eHealth and home-sampling.

Target group

MSM

This thesis is focused on men who have sex with men (MSM) as most new HIV/STI infections occur in this group. The results and conclusion presented in this thesis are of importance for all MSM who are sexual active, have unprotected sex and in need of regular HIV/STI testing. Especially MSM who do not get tested regular, do not feel comfortable visiting STI clinics, or have other barriers towards location-based testing, will benefit from our innovative home-care program, as addition to regular sexual healthcare. Currently, we are further developing the home-care program described in this thesis to make the program available for a broader MSM population.

Healthcare providers

The results of this thesis are relevant for health policy makers, public health professionals from STI clinics, HIV hospital clinics, and general practitioner (GP) offices. It is important to recognise and involve healthcare providers so that interventions and innovations can evolve accordingly and provide adequate and meaningful support. Collaborating and sharing with other HIV/STI care providers would improve sexual healthcare in general and fa-

cilitates relations and etworks with low-threshold knowledge sharing and improved patient management. Policy makers are also a target group, especially regarding their role in designing and implementing guidelines and healthcare programs.

Future

Limburg4Zero

The knowledge gained from the studies describes in this thesis form the base of a new regional project for MSM to move to zero new HIV diagnoses in Limburg. This program, called 'Limburg4zero', aims to develop, implement and evaluate an integrated and regional-focused approach to engage high risk groups in HIV and sexually transmitted infections (STI) testing, treatment, and care. In this project, home-sampling HIV/STI test will be used to increase HIV/STI testing among MSM combined with sexual health care (counseling on safe sex, PrEP, and (early) treatment). To engage MSM, care providers, societal organizations, and Universities collaborate to implement innovative strategies that overcome testing-barriers (e.g. time, stigma)

In the pilot implementation we encountered issues with syphilis diagnosis. Based on experience with home-sampling from our implementation, our research group is currently exploring innovative diagnostics to optimize blood sampling and use of available blood to test for syphilis. In our development and pilot implementation, a strong network between care providers is established. This network enables a logistical infrastructure to enable testing, prevention, and care for MSM and a collaborative infrastructure to enable support/information-exchange between care-providers. Successful elements of our integrated approach will be included in regular HIV/STI care, for a sustainable implementation after the project.

PORTFOLIO

Publications

Leenen, J., Hoebe, C. J. P. A., Ackens, R. P., Posthouwer, D., van Loo, I. H. M., Wolffs, P. F. G., & Dukers-Muijrers, N. H. T. M. (2020). Pilot implementation of a home-care programme with chlamydia, gonorrhoea, hepatitis B, and syphilis self-sampling in HIV-positive men who have sex with men. *BMC Infectious Diseases,* 20(1), 1-9

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Presentations

International

International Union against Sexually Transmitted Infections (IUSTI), Dublin, Ireland – 2018
International Symposium on Human Chlamydial Infections (ISHCI), Zeist, The Netherlands -2018

National

Research day medical microbiology, Maastricht - 2019
Annual Amsterdam Chlamydia Meeting (AACM), Amsterdam - 2017
Research day medical microbiology, Maastricht - 2017
National HIV/AIDS conference, Amsterdam - 2017

Courses and training

Project Management: From Theory to Practice
Utrecht Summer School - 2019
PRINCE2® certificate

Research Writing
University Maastricht - 2018

Intervention Mapping
University Maastricht - 2017

Teaching

Supervising Master students
Institutional supervisor
Olivia Rolly, Master program Healthcare Policy, Innovation & Management - 2019
The economic impact of Chlamydia trachomatis infection in high-income countries: a systematic review

Institutional supervisor
Mark Pater, Master program Medicine - 2018
Procesevaluatie van zelfafname SOA testen van de GGD voor HIV+ MSM

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WE DO NOT SEE THINGS AS THEY ARE,

WE SEE THINGS AS WE ARE