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SCREENING FOR HEPATITIS C VIRUS INFECTION OF INDIVIDUALS AT RISK HIDDEN AMONG THE GENERAL POPULATION

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CONTENTS

LIST OF ABBREVIATIONS

ALT	alanine transferase
AST	aspartate transferase
CDC	Centers for Disease Control and Prevention
CHC	chronic hepatitis C
CI	confidence interval
DAA	direct-acting antiviral (agents)
DBS	dried blood spot
DU	drug use
EVR	early viral response
Exp	explosion search
GP	general practitioner
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HDI	human development index
HIV	human immunodeficiency virus
IRB	institutional review board
IQR	interquartile range
IDU	injecting drug use
IL28B	interleukin-28B
MeSH	medical subject headings
MSM	men who have sex with men
NIDU	non-injecting drug use
NTA	negative testing advice
OR	odds ratio
PAT	parenteral antischistosomal therapy
PCR	polymerase chain reaction
PTA	positive testing advice
PTPD	post-test probability of disease
RVR	rapid viral response
SD	standard deviation
SMS	short message service
STD	sexually transmitted disease
STI	sexually transmitted infection
SVR	sustained virological response
TMA	transcription-mediated amplification
VA	veterans affairs
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

Adapted from:

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A Kok, FR Zuure, CJ Weegink, RA Coutinho, M Prins. Hepatitis C in Nederland: schaarse gegevens over actuele prevalentie en de noodzaak van epidemiologisch onderzoek en innovatieve opsporingsmethoden. *NTvG 2007;151(43):2367-2371*

1.1 Hepatitis C virus

Hepatitis C virus (HCV) infection is caused by a mainly bloodborne virus and was first identified in 1989. It affects an estimated 2-3% of the world's population [1]. Approximately 75% of HCV infections progress to chronic infection, posing the patient at risk for the development of cirrhosis, liver cancer, and death [2;3]. In chronically infected patients, the onset of HCV itself and the development of cirrhosis are usually asymptomatic [2;4]. Therefore, many infections remain undetected or are diagnosed late. HCV infection was the most common cause of post transfusion non-A/non-B hepatitis, as it was especially recognized among individuals who had received contaminated blood products. In 1991, the first commercial HCV antibody test became available, leading to a dramatic decrease in the incidence of transfusion-acquired HCV infection in countries that introduced the routine screening of donor blood [4]. However, based on mathematical modeling, it has been estimated that HCV-related morbidity and mortality will at least double over the next two decades in various medium- to high-income countries [5;6]. Three quarters of liver cancers worldwide are related to chronic hepatitis B virus (HBV) and HCV infections [7]. In both Europe and the United States, HBV and HCV-infection related mortality exceeds that of HIV [8;9].

Global pattern

The World Health Organization (WHO) estimates that the African and Eastern Mediterranean regions have the highest prevalence of HCV infection, but reliable population based studies are lacking for many countries [1]. The world's highest prevalence of HCV infection in the general population (15-20%) has been reported in Egypt, as a result of injection therapy against schistosomiasis in mass settings without sufficient sterilization of reused injection materials [10;11]. Although health-care associated HCV transmission incidentally occurs in high-income countries, its current contribution to the overall prevalence in these countries is low [12]. In contrast, non-sterile injection practices, lack of HCV screening of donor blood, and other iatrogenic routes still account for a significant route of HCV transmission to the general population in medium- and low-income countries [13].

In most high-income countries, prevalence of HCV infection among the general population is low. In the Netherlands, HCV prevalence in the general population has been estimated at 0.22% (min: 0.07%; max: 0.37%) [14] and somewhat higher in the larger cities [15]. Non-western migrants and (former) injecting drug users are considered to account for the majority of HCV infections in the Netherlands [14].

Risk groups for hepatitis C virus infection

Injection drug users are at high risk of HCV-infection (prevalence 60 to >80% [16]). Other risk groups for HCV-infection are those who received blood products before 1992 (i.e., hemophiliac patients, prevalence ~70% [17]); hemodialysis patients (prevalence 3 to 23% [18]); individuals who underwent non-sterile medical procedures abroad (prevalence unknown); non-injection drug users (prevalence 2 to 35%), though the causal pathway to infection in this group remains unclear [19]; individuals who experienced a needle-stick injury and health-care professionals dealing with patient blood (prevalence unknown) [20]; household contacts with HCV-infected individuals (possible transmission through the shared use of toothbrushes, razors, etc, prevalence 0 to 11% [4]); and children born to HCV-infected mothers, with transmission rates of ~4%, increasing in maternal HCV/HIV co-infection to ~20% [21]. Other activities that may cause blood-blood contact have been identified as possible routes for HCV infection, such as tattooing, body piercing, and cultural/

religious practices (e.g., scarification, circumcision, acupuncture). However, results are inconsistent and it is uncertain whether these risk factors make any measurable contribution to overall HCV transmission [22;23].

Even in the presence of HIV co-infection, HCV is rarely transmitted through heterosexual intercourse [24]. Since 2000, however, HCV infection has emerged among HIV-infected men who have sex with men (MSM) [25]. Most infected MSM denied injecting drug use. It has been suggested, mainly through case studies, that HCV infection is associated with HIV-infection, presence of ulcerative sexually transmitted diseases, sexual techniques causing mucosal damage, and sex under the influence of non-injecting drugs [25]. Phylogenetic analyses have shown clusters of MSM-specific HCV strains, indicating a sexual route of HCV transmission [25].

Clinical course of infection

In the majority of cases acute HCV infection is asymptomatic. Less than one third of individuals with an acute HCV-infection experiences mostly mild and aspecific symptoms such as a loss of appetite, fatigue and flu-like symptoms, and occasionally jaundice [26]. The majority (~75%) of patients develop chronic HCV infection [3], defined as the persistence of HCV RNA after 6 months of infection. Approximately 20 years after onset of chronic HCV infection, the infection may lead to liver cirrhosis in 6-25% of patients, 1-4% of whom develop hepatocellular carcinoma per year [27-29]. Several host-related and external factors have been associated with accelerated HCV disease progression, such as male sex, heavy alcohol intake, elevated alanine transferase (ALT), higher grade of histological inflammation, HIV coinfection, and genetic factors [28;30-33]. Although HCV infection is a slowly progressing disease, it is the main cause of liver transplantations in the US and Europe [34].

Molecular epidemiology

HCV is a single stranded RNA virus. The high genetic variability of the HCV genome has led to a classification of the virus in six major genotypes (1 to 6), which, except for genotype 5, are each further divided into more than 80 related subtypes (a,b,c,…) [35;36]. As HCV genotype distribution varies over time and depends on geographic area and mode of transmission, it provides clues about the historical origin and spread of the virus. Some HCV subtypes are found globally, due to a swift spread in the 20th century through needle sharing among injecting drug users (types 1a and 3a), and contaminated blood products (types 1b, 2a and 2b). These genotypes represent the majority of infections in Europe and Northern-America. In contrast, the presence of numerous and highly diverse subtypes in western/central Africa and the Middle East (genotypes 1, 2 and 4) as well as Southeast Asia (genotype 3 and 6) suggest that these genotypes originate from these areas where they have been endemic for a long time [37-39].

Therapy

Recently, important advances in the treatment of chronic HCV infection have been made. Boceprevir and telaprevir, two HCV-protease inhibitors, have recently become available and have demonstrated significant improvements in the effectiveness of treatment of HCV genotype 1 infections [40;41]. Currently, the recommended therapy for HCV infection consists of the use of a modified form (pegylated) of interferon alpha (protein with immunomodularity and antiviral properties) and ribavirin (a nucleoside analogue with antiviral activity), in combination with boceprevir or telaprevir for HCV genotype 1 infections [42]. HCV treatment duration is usually 24 weeks (genotype 2 and 3), or 48 weeks (genotype 1 and 4) [43]. In patients with baseline HCV RNA <600,000 IU/ml and

in patients without cirrhosis treated with boceprevir or telaprevir in addition to peginterferon and ribavirin, response-guided therapy can result in a shortened duration of therapy (i.e., 12-16 weeks for genotype 2 and 3, 24-28 weeks for genotype 1 and 4) [42;43]. The aim of treatment is to eradicate viral RNA and to reach a sustained virological response (SVR), which is defined as the absence of HCV RNA at 24 weeks after the end of treatment [44].
One of the most important predictors of SVR, which occurs in 42-90% of the cases, is HCV genotype [45]. Genotype 4 is a difficult-to-treat genotype, with approximately 50% of treated patients achieving SVR [43], compared with an SVR up to 65-75% for genotype 1-infected patients who are treated with standard therapy plus boceprevir or telaprevir [40;41], and up to 80-85% in patients with genotypes 2 and 3 [46]. Other predictors of therapeutic outcome that may influence treatment duration include interleukin-28B (IL28B) polymorphisms (especially for genotype 1 and 4 patients), low HCV RNA level prior to treatment, rapid viral response (RVR) (undetectable HCV RNA levels at week 4), and early viral responses (EVR) (≤2 log decrease in viral load during the first 12 weeks) [45;47]. Approximately 10-14% of all patients discontinue treatment because of serious side effects such as influenza-like symptoms and neuropsychiatric symptoms [44]. All patients should be considered for treatment. However, patients with mild disease activity may defer therapy as future treatment of chronic HCV infection will probably be more effective and of shorter duration [48]. The further development of direct-acting antiviral (DAA) agents and drugs targeting host cell factors that are essential for efficient HCV replication indicate a promising future for the treatment of HCV infection.

Prevention and control

In contrast to hepatitis B virus (HBV), for HCV there is no vaccine available, nor are there drugs for post-exposure prophylaxis or prevention of mother-to-child-transmission. Prevention relies completely on precautionary measures preventing further spread. In low- and medium income countries, improvement of blood transfusion safety and health-care conditions are important for reducing HCV transmission. In high-income countries, screening of donor blood products in 1991 significantly reduced the incidence of iatrogenic HCV transmission. In the Netherlands, incidence of HCV infection among drug users has declined, most likely due to decreasing injection risk behavior, probably resulting from comprehensive harm reduction programs including needle exchange programs and methadone provision [49;50]. In HIV-infected MSM, a group in which incidence of HCV infection has increased in recent years [51;52], HCV infection could be prevented through condom use and hygienic measures when practicing rough sexual techniques that could cause mucosal damage. Since in many high-income countries incidence of HCV infection is low and effective treatment is widely available, identification of those who became infected in the past is of major importance to reduce future HCV-infection related morbidity and mortality. Besides treatment, these individuals can benefit from vaccination against hepatitis A virus (HAV) and HBV infection, and can adjust their lifestyle (e.g., limiting alcohol use) which can improve prognosis of HCV infection.

Screening for hepatitis C virus infection

Standard HCV testing includes screening for anti-HCV antibodies using an anti-HCV EIA confirmed by immunoblot or HCV-RNA testing. In a clinical setting, a positive anti-HCV test is directly followed by RNA testing to establish the presence of ongoing infection. In the case of a potentially acute infection, RNA testing will be done since it might take several weeks (20-150 days) before HCV antibodies develop [53]. In immunosuppressed patients (e.g., HIV-infected individuals) HCV antibody seroconversion can be delayed, or HCV antibody may even remain undetectable despite HCV viremia [54;55].

Because of the asymptomatic onset and disease in the first decades of HCV infection, many HCV-infected individuals are not aware of their condition and therefore do not seek help or perceive a need to screen for HCV infection. As a result, a potentially large number of infected individuals are still unidentified. Diagnosis of these individuals is vital to treatment and prevention of future HCV-infection related morbidity and mortality. In high-income countries, the Wilson and Jungner criteria for screening are considered applicable for chronic HCV infection [56]: HCV infection is considered to be an important health problem; there is an accepted treatment for patients with recognized disease; facilities for diagnosis and treatment are available; there is a recognisable stage of disease; there is a suitable and acceptable test for diagnosis of HCV infection; the natural history of HCV infection is understood; there is an agreed policy on whom to treat as patients; treatment is considered cost-effective; and case-finding should be a continuing process and not a 'once and for all' project [57].

There are several types of screening strategies such as case finding (i.e., opportunistic screening [58]), mass population screening, and selective screening. As HCV spread among individuals who received contaminated blood products before the introduction of the first HCV antibody test in 1991, various high-income countries introduced look-back programs in which recipients of blood products from HCV-infected donors were notified and encouraged to be tested [59;60]. The costs, however, were high and the yield low [61;62]. Selective screening of risk groups for HCV infection has been recommended [63;64]. Some of the high risk groups for HCV infection are relatively easy to reach and have been targeted by screening programs as part of specialized medical care (e.g., current drug users on methadone treatment [65;66], HIV-infected individuals receiving clinical care [67], and hemophiliac patients [68;69]). However, other risk groups are more difficult to target for screening. For example, persons at risk for HCV infection through occasional injecting drug use in the remote past will not attend programs targeted at active drug users and might not identify themselves as being at risk for HCV infection. The same holds true for individuals who received a blood transfusion before 1992. These risk groups can be considered hidden among the general population. The size of this hidden population may be substantial. A recent study estimated that of the total population of HCV-infected individuals in the Netherlands, only 34% are in relatively easy to reach high-risk groups such as hemophiliac patients, HIV-infected patients, and current injecting drug users; 41% are first-generation migrants and 25% belong to other risk groups [14].

Hepatitis C screening of risk groups hidden within the general population

A few studies have evaluated screening tools for determining risk for HCV infection (e.g., establishing individual risk for HCV infection as a condition for screening) to support efficient screening of the hidden population of HCV-infected individuals in healthcare facilities [70-72]. Such selective screening is promising and more affordable than mass screening [73;74], but the use of these tools will not reach the pool of undiagnosed HCV-infected individuals who do not visit such facilities. In many countries, the general practitioner (GP) is an essential part of medical care, and the first point of contact for most medical services. However, HCV awareness, testing, and referral for those who test positive in the GP clinic has been suboptimal [75-78]. A study showed that even when risk factors for HCV infection were documented, a small proportion of those at risk was screened [75].

Hepatitis C screening in the Netherlands

Soon after the first HCV antibody test became available, in 1992, the Blood Transfusion Council of the Netherlands Red Cross advised hospitals to inform recipients of HCV-infected donor blood and offer them screening. As in many other targeted look-back programs, the yield was limited as only a relatively small number of recipients could be traced, and a large proportion of those had already died [79;80].

Routine HCV screening was introduced in care programs for various high risk groups such as active injecting drug users and hemophiliac patients in the Netherlands. Awareness for HCV infection among the general population was low. In 1997, the Health Council of the Netherlands recommended that populations at risk for HCV infection should be identified and provided with information, and that epidemiological research should be conducted in order to gain additional insight regarding how HCV infections can best be identified and prevented in the Netherlands [79]. In 2004, the Health Council reiterated the urgency of this recommendation given the improved treatment options for chronic HCV infection [81]. In accordance with these recommendations, epidemiological research was conducted [e.g., 14;15;23;82-85] and several HCV screening programs targeting risk groups in the general population were initiated in the Netherlands.

1.2 Facilitation of hepatitis C screening of individuals at risk hidden among the general population

This thesis focuses on two of the HCV screening programs that have been carried out in the Netherlands. One of them is a risk- and Internet-based screening pilot program, described in 1.2.1 and in more detail in chapter 3. The other is a community-based HCV and HBV screening program targeting first generation Egyptian migrants (see 1.2.2 and chapter 4). In both programs, screening was organized beyond the GP clinic. The evaluation of screening beyond the GP clinic was considered useful for two reasons. First, not all individuals visit their GP regularly, and the time that individuals generally spend with their GP is short. In the Netherlands, in 2010, 72.3% of the population visited a GP at least once, with a mean number of 5.9 GP visits in that year [86], each taking about 10.2 minutes [87]. Hence, it is unlikely that GPs are aware of all of their patients' risk factors for HCV infection or have time to investigate these during their consultations. Second, those who practiced experimental injecting drug use in the past, including those who injected only once, present a group at increased risk for HCV infection that may not easily disclose their past injecting behavior to their GP. In the following paragraphs the background, rationale, and organization of the internet-based and community-based programs are outlined.

1.2.1 Use of the Internet for the promotion of hepatitis C screening

With the advent of the Internet as a popular communication platform in many high-income countries, new possibilities arose for health care professionals to not only distribute up-to-date information 24 hours a day, 7 days a week, but also to reach and interact with a large audience beyond the setting of health care facilities, and to provide low threshold access to health care services. Internet use in health care has been defined as 'eHealth': "*an emerging field in the intersection of medical informatics, public health and business, referring to services and information delivered or enhanced through the Internet and related technologies*" [88]. The interactive nature of the Internet offers the possibility to tailor information and services to the needs of the individual. Research has shown that tailored health information can be more effective than generic information in establishing health behavioral change, such as healthy dieting [89] or mammography screening [90]. For HCV infection, a stigmatized disease that is associated with drug use, the discrete character of the Internet may appeal to those who wish to get tested anonymously. Considering these advantageous characteristics, the Internet was considered a potentially useful medium, through which to provide a self-selecting tool for the identification of risk groups for HCV infection and arrange a testing trajectory for those at risk for infection.

Besides the advantages relative to other media, the reach of the Internet throughout the general population increases its potential effectiveness. The Netherlands are among the countries with the highest Internet penetration rate in Europe. In 2012, the Internet penetration rate reached almost 93%, representing over 15.5 million Dutch Internet users [91]. The majority uses the Internet on a daily basis, at home, and more than 50% indicated to have searched for health related information in the past three months [92]. Internet use has virtually spread throughout the Dutch population. Only among the elderly and those with lower education Internet access is somewhat lower, estimated at 61% among those aged 65-75 versus 91% or higher in the younger age groups, and 85% among those with low educational levels versus 97% and higher among those with higher educational levels [92]. Data from 2005-2009 indicate that Internet access, use and skills among migrant groups has increased, equaling that among the native Dutch population [93]. Therefore, eHealth offers a good opportunity to facilitate HCV screening for a large audience in a relatively anonymous way.

Organization of the Internet-based screening program

With the potential advantages of the Internet in mind, we set up a screening program for HCV for risk groups that are hidden among the general population. The program aimed to inform individuals about their personal risk for HCV infection by offering them an interactive online questionnaire assessing risk for HCV infection through structured multiple-choice questions that addressed the prominent risk factors for infection. The questionnaire was available in six languages (i.e., Dutch, English, Spanish, French, Turkish and Arabic) to facilitate participation of first-generation migrants without sufficient knowledge of the Dutch language. Those who reported at least one risk factor for HCV infection were informed and advised to seek HCV blood testing. When they were living in the project's pilot regions Amsterdam and South Limburg, they were offered a low-threshold testing procedure; they could visit one of the associated laboratories for a free and anonymous blood draw and obtain their test results within a week, via the Internet. Those found with a reactive test result were offered a face-to-face follow-up trajectory at their Public Health Service in which a confirmation anti-HCV antibody blood test and, if positive, follow-up HCV-RNA testing were arranged. For those with a chronic HCV infection, referral to a hepatologist was arranged. The program was promoted through regional media campaigns.

Health behavior theory and hepatitis C screening

In order to promote participation in our screening program, the program incorporated information and features that addressed (potential) determinants of health behavior as derived from health behavior theories. Health behavior theories help to understand why people do or do not follow public health and medical advice, and give insight into factors that can be modified to promote healthy behavior [94]. Research has shown that health promotion programs that are theory-based are more likely to be effective than those without a theoretical base [95]. Therefore, concepts from the revised health belief model, the theory of planned behavior, and the extended parallel process model were applied to the Internet-based HCV screening program.

Revised health belief model

One of the most widely used theoretical models is the health belief model. This model was developed in the 1950s to explain screening and disease detection behavior in people in response to a disease threat [96]. Today, the revised health belief model is applied more broadly, and is used to explain why people take action to prevent, detect, or control a disease. The health belief model focuses on perceived severity of and vulnerability to a disease (perceived threat), perceived barriers to and benefits of executing the preventive behavior (expectations regarding the outcomes of the positive

health behavior), perceived self efficacy (the degree to which one perceives oneself capable of executing the health behavior), and cues to action (external stimuli which activate 'readiness to act' and stimulate the execution of the health behavior).
For HCV infection, awareness among the general population is relatively low. Hence, for the majority of those at risk for HCV infection, the infection will be perceived as a new emerging health threat that does involve apparent physical symptoms. In that context, the health belief model is particularly relevant for explaining HCV screening behavior, because of its beliefs related to perceived threat. Applied to the context of HCV screening, the likelihood of HCV testing increases when perceived threat of HCV infection is high, perceived barriers of testing are low, perceived benefits of testing are high, self efficacy for testing is high, and relevant cues to action are present.

Theory of planned behavior
Another widely used theory is the theory of planned behavior that evolved from the theory of reasoned action. According to the theory of planned behavior, attitudes (personal evaluations of the behavior based on behavioral beliefs), subjective norms (perceptions of other people's evaluations of the behavior based on normative beliefs), and behavioral control (perceived control over the execution of the behavior based on control beliefs; similar to self-efficacy) determine the intention to engage in a behavior [97]. Behavioral intention is presumed to best predict behavior. However, actual behavioral control (e.g., lack of control due to environmental factors) can also directly influence behavior. Applied to the context of HCV screening, the intention to take an HCV test increases when attitudes towards testing are positive, when subjective norms favor HCV testing, and when perceived behavioral control is high.

Extended parallel process model
The extended parallel process model also focuses on health beliefs but is more specific than the health belief model with regard to the role of emotion in responses to a perceived health threat. According to the extended parallel process model, health threats can cause individuals to engage in either danger control or fear control processes. Danger control is aimed at reducing the health threat through cognitively processed adaptive responses (e.g., seeking testing and treatment), whereas fear control is aimed at reducing unpleasant feeling related to the health threat. Fear control often results in maladaptive responses such as message avoidance and defensive reactions (e.g., denial of risk). Whether individuals engage in danger or fear control processes depends on the degree to which threat, self efficacy, and response efficacy (the extent to which the recommended behavior is expected to effectively reduce the threat) are perceived to be present [98]. Medium to high perceived threat combined with high perceived efficacy will most likely result in danger control responses while high perceived threat combined with low perceived efficacy will most likely lead to fear control responses. Applied to the context of HCV screening, the extended parallel process model would suggest that the likelihood of HCV testing is greatest when individuals perceive the threat of HCV infection as moderate to high and possess high levels of perceived self efficacy and response efficacy.

Application of theory to the Internet-based screening program

Various concepts from the theoretical models described above were operationalized through the screening program. Our communication attempted to increase sense of vulnerability. For example, through communication of risk factors for acquiring HCV infection, possibility of infection without any experience of symptoms, and provision of information that was tailored to individuals' reported risk factor(s). We aimed to increase sense of perceived severity, for instance by addressing the

potential severe long time health outcomes of chronic HCV infection. For increased understanding of the benefits of testing, factors such as the availability of treatment were mentioned. In the project we also aimed to increase sense of perceived self efficacy by communicating the ease with which personal risk for HCV infection can be assessed, and the low threshold blood testing procedure that allowed individuals confronted with threatening information to take a test the next working day. Email and SMS reminders were sent, in order to provide cues for action.

Research objectives

The aim of the Internet-based screening program for HCV was to identify individuals at risk for HCV infection, to motivate, and arrange for them to go for HCV testing. The key research objective was to evaluate whether a hidden population of individuals at risk for HCV infection could be reached through a public media information campaign combined with an Internet screening tool. More specific research objectives were to evaluate:

- the reach of the media campaign in attracting those potentially at risk for HCV infection to the project's website;
- the extent to which those who completed the risk assessment questionnaire were at risk for HCV infection, and their characteristics;
- the blood test uptake and determinants of test uptake among those at risk;
- reasons for complying or not complying with test advice that was given online;
- the proportion of individuals that tested positive for HCV infection and their characteristics;
- the clinical outcomes of the screening;
- and the usability and acceptability of the service as perceived by the participants.

1.2.2 Community-based outreach to promote hepatitis C screening

The Internet-based screening program aimed to offer an anonymous screening service to attract a hidden population of individuals at risk for HCV infection such as former injecting drug users, those who received a blood transfusion in the past, and also migrants at risk. The latter group however was underrepresented in the Internet program. We hypothesized that this group may be better reached through a community-based program. Because of their shared background and common characteristics such as religion and culture, migrants may be identified at venues specific to their community, such as churches and mosques. Therefore, we set up a program for first-generation migrants from Egypt (see chapter 4).

Theory of community based health programs

A community can be recognized as a unit of identity [99]. The sense of community, i.e., the sense of belonging to and of sharing common desires with other members [99], can vary between weak and strong and is based on aspects of membership, influence over what occurs within the community, shared values and needs fulfillment, and a shared emotional connection [100]. A strong sense of community is associated with community mobilization, whereas community heterogeneity reduces engagement and participation [99]. Hence, the sense of community ("community focus") is an important principle to acknowledge when planning a community-based screening program. Another important principle on which many community-based health programs are based is the beneficial result of community member participation. Although there is little evidence that community involvement is associated with program effectiveness [99], collaboration between health program planners and community leaders, and active participation of those community leaders and participants in the health program are increasingly valued [100]. Theory assumes that participation increases individual empowerment

and serves as a method to incorporate community values and attitudes into the program. More importantly, when a program is supported by community leaders, it can increase local confidence in the benefits of the program and therefore may become more acceptable to the community members [99]. Besides community member participation, intersectoral collaboration in the health program (i.e., collaboration among different community organizations), the availability of substantial resources and a long term program view, and a multifaceted intervention addressing both behavioral and environmental components are assumed to increase the effectiveness of community-based health programs [99].

Organization of the community-based screening program

The community-based screening program was designed for first-generation migrants from Egypt living in the Amsterdam region. Migrants comprise a group at increased risk for HCV infection (and other infectious diseases such as HBV infection) because of their increased risk of exposure to risk factors in their country of origin before migration. The program focused on migrants from Egypt, since Egypt is the country with the world's highest prevalence of HCV infection (nearly 15%) [11]. Although data on the prevalence among migrants was lacking, we considered that screening this population would be useful to detect undiagnosed infections and bring infected individuals into health care. First-generation Egyptian migrants represent an ethnic minority community in the Amsterdam region with an estimated size of 3200 adults. We considered the community sense to be relatively strong, and even stronger for sub-communities on the basis of religion (i.e., Coptic and Islamic Egyptians).

We actively involved the Egyptian community in the screening program. In order to increase the potential reach of the program and create community-wide awareness for HCV infection, various community organizations were approached to discuss HCV infection and the proposed screening program (e.g., a Coptic church, an Islamic mosque, an Egyptian trade organization, a Sunday school, and an organization for Egyptian women). The attempts were successful; community leaders agreed to participate in the organization and promotion of the program, and provided accommodation for educational and screening sessions. Moreover, collaboration with the community leaders highlighted the community's desire to organize simultaneous screening for both HCV and HBV. Egypt is a medium endemic country for HBV infection, risk factors for HCV and HBV infection overlap, and HCV and HBV infection are often confused (that is, people are often not aware of the differences between the two virus infections). Therefore, HBV screening was incorporated into the program. The screening was free of cost for participants, and was promoted via announcements by the community leaders and flyers which were distributed through the community organizations. All information materials were in both Dutch and Arab, and native Arab speaking educators had a central role in the program. It was considered that, although most first-generation migrants from Egypt are highly educated and have sufficient knowledge of the Dutch language, migrants may better express themselves in their native language, especially with regard to sensitive topics [101]. The educators were trained on the topic of viral hepatitis and led the educational sessions. They highlighted transmission routes, potential symptoms, the epidemic in Egypt, treatment options and prevention measures. During the testing sessions they were present to answer participant questions.

Research objectives

The aim of the community-based screening program for HCV and HBV infections was to identify undiagnosed infections and bring these individuals into care. More specific research objectives were to evaluate:

- the reach of the program in attracting first-generation migrants from Egypt;
- the prevalence of HCV and HBV infections and determinants of infection;
- the clinical outcomes of the screening;
- and the phylogenetic evidence for infection acquisition before migration.

1.3 Thesis outline

This thesis describes and discusses the feasibility and effectiveness of HCV screening programs targeting risk groups in the general population, focusing in particular on the Internet-based and the community-based approach.

Chapter 2 describes the results of a systematic literature review that summarizes characteristics and outcomes of international HCV screening programs for risk groups for HCV infection that are hidden in the general population.

Chapter 3 describes three studies that cover the development and results of the Internet-based screening program for HCV. In the first study, a risk assessment questionnaire for HCV infection was developed and evaluated using liver patients with a known HCV infection status. The second study describes the implementation of that questionnaire as an online pre-screening selection tool in an HCV screening service targeting risk groups hidden among the general population, and the outcomes of that service. The third study describes the results of qualitative research on reasons for compliance and noncompliance with the HCV test advice obtained through the online risk screening tool, and focuses particularly on the role of the online blood testing procedures in that process.

Chapter 4 describes the results of the community-based screening program for HCV and HBV aimed at first generation Egyptian migrants.

Chapter 5 concludes with a general discussion and summarizes the work described in this thesis.

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CHAPTER 2

EVALUATION OF HEPATITIS C SCREENING PROGRAMS WORLDWIDE

CHAPTER 2.1

Outcomes of hepatitis C screening programs targeted at risk groups hidden in the general population: a systematic review

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Abstract

Objective: Effective screening programs are urgently needed to provide undiagnosed hepatitis C virus (HCV)-infected individuals with therapy. This systematic review of characteristics and outcomes of screening programs for HCV focuses on strategies to identify HCV risk groups hidden in the general population.

Methods: We conducted a comprehensive search of MEDLINE and EMBASE databases for articles published between 1991-2010, including studies that screened the general population using either a newly developed (nonintegrated) screening program or one integrated in existing health care facilities. Look-back studies, prevalence studies, and programs targeting high-risk groups in care (e.g., current drug users) were excluded.

Results: After reviewing 7052 studies, we identified 67 screening programs: 24 non-integrated; 41 programs integrated in a variety of health care facilities (e.g., general practitioner); and 2 programs with both integrated and nonintegrated strategies. Together, these programs identified approximately 25700 HCV-infected individuals. In general, higher prevalence of HCV infection was found in programs in countries with intermediate to high prevalence of HCV infection, in psychiatric clinics, and in programs that used a prescreening selection based on risk factors for HCV infection. Only 6 programs used a comparison group for evaluation purposes, and 1 program used theory about effective promotion for screening. Comparison of the programs and their effectiveness was hampered by lack of reported data on program characteristics, clinical follow-up, and type of diagnostic test.

Conclusions: The published studies identified a relatively small proportion of the estimated HCV-infected population. A prescreening selection based on risk factors can increase the efficiency of screening in low-prevalence populations, and we need programs with comparison groups to evaluate effectiveness. Also, program characteristics such as type of diagnostic test, screening uptake, and clinical outcomes should be reported systematically.

Introduction

Hepatitis C virus (HCV) infection, primarily a blood-borne virus and first identified in 1989, is a major public health problem. Worldwide an estimated 123 million individuals are HCV-antibody positive (1), of whom approximately 75% are chronically infected and at risk for the development of cirrhosis, which can lead to liver cancer and death (2;3). In chronically infected patients, the onset of HCV infection and the development of cirrhosis are usually asymptomatic (2;4); many infections remain undetected or are diagnosed at a late stage. In the United States of America (USA), an estimated 43% to 72% of HCV infections are undiagnosed (5-7). In 2001, successful combination therapy for HCV infection became widely accessible (8-12) and more effective therapeutic options are becoming available (13;14). Effective screening programs are urgently needed to provide undiagnosed HCV-infected individuals with therapy and to spread information about preventive measures that each person should take (e.g., reducing alcohol intake, other precautionary measures against further spread), thus decreasing future morbidity and mortality.

There are several types of screening strategies such as mass population screening, selective screening, or case finding (i.e., opportunistic screening (15)). Selective screening of risk groups for HCV infection (see Box 1) has been recommended (16;17). Some of the high risk groups for HCV infection are relatively easy to reach and have been targeted by screening programs as part of specialized medical care (e.g., current drug users (DUs) on methadone treatment (19;20), hemophiliacs (21;22), and HIV-infected individuals receiving clinical care (23)). However, other risk groups are more difficult to target for screening. For example, persons at risk for HCV infection through occasional IDU in the remote past will not attend programs targeted at active drug users and might not identify themselves as being at risk for HCV infection. The same holds true for individuals who received a blood transfusion before 1992. These groups can be considered as 'hidden risk groups' among the general population. The size of this hidden population may be substantial. A recent study estimated that of the total population of HCV-infected individuals in a high-income country, only 34% are in relatively easy to reach high-risk groups such as hemophiliac patients, HIV-infected patients, and current IDU; 41% are first-generation migrants and 25% belong to other risk groups (24).

Finding an effective strategy to identify the hidden population of undiagnosed HCV-infected individuals is challenging. An overview of screening programs for HCV infection provides insight into strategies that have been used so far and their outcomes, and can provide insight into the best way forward. In our review, we systematically review characteristics and outcomes of screening programs for HCV infection targeted at risk groups hidden in the general population. We focused in particular on the promotion of the screening program, whether or not prescreening selection criteria were used, and the use of psychosocial theory or knowledge about determinants facilitating participation in screening programs, since health promotion programs that are based on theory are more likely to be effective than those that are not (25). We discuss the implications of these findings for future screening strategies for HCV infection.

Box 1: Risk groups for HCV infection (16, 17)

- Individuals with a history of injecting drug use (IDU), including those who injected only a limited number of times many years ago and do not consider themselves to be drug users
- Individuals who received clotting factor concentrates produced before 1987 or a blood transfusion or an organ transplant before 1992 including hemophiliac patients (systematic screening of blood donors for HCV antibodies was introduced in 1991) (18)
- Individuals with occupational exposure to infected blood
- HIV-infected men who have sex with men (MSM)
- Chronic hemodialysis patients
- Children born to HCV-infected mothers

Methods

Search strategy

We searched in the MEDLINE (PubMed) and EMBASE databases for articles published in any language before July 27, 2010. A comprehensive strategy was used to include all possible studies in which individuals were screened for HCV. Search terms included hepatitis C (Medical Subject Headings [MeSH] for PubMed and Explosion search [Exp] for Embase) or HCV or "hepatitis C" in title or abstract combined with search terms in title or abstract that reflect screening (i.e., mass screening [MeSH/Exp], screen*, "case finding*", "case identification*", "case detection*", "hepatitis C testing", "HCV testing") or search terms in title or abstract and/or MeSH/Exp that reflect campaigns or evaluation of health programs (i.e., campaign*, health promotion, health service*", feasibility, pilot*, "program* evaluation*", "program* effect*", "*health care quality"). The search was limited to articles published after 1990 since a more sensitive second-generation HCV antibody test was introduced in 1991 (26). The complete search strategy including truncation characters is available from the authors. In addition, we screened the reference lists of the articles that were included in the prefinal selection for potentially relevant publications.

Study selection

Studies were included if they reported screening of individuals in the general population, including screening in primary care facilities that are not related to specific risk groups for HCV infection. Exclusion criteria pertained to 'look-back' studies, in which recipients of HCV-infected donor blood are notified and offered screening and studies conducted in specific, identifiable risk groups for HCV that are in specialized care: current drug users, HIV-infected individuals, incarcerated individuals, hemodialysis patients, or multitransfused patients such as hemophiliac patients. In addition, studies were excluded if 1) the study was designed to assess the prevalence in a given population, and/or 2) if the study was undertaken to investigate transmission rates and determinants (e.g., mother-to-child transmission (27)) or the association between HCV infection and another medical condition (e.g., diabetes (28;29)), and/or 3) nothing was reported about notification, referral, or medical follow-up of participants. The latter criterion did not apply to studies describing HCV screening at the general practitioner (GP) clinic, since notification of results in this setting is considered to take place. Articles in languages other than English, French, German, or Spanish were excluded if there was no English abstract of if the English abstract did not yield enough data.

The first selection round was based on title and abstract (if available) only and was done by four

authors (Freke Zuure, Anouk Urbanus, Charles Helsper, and Charlotte van den Berg). The database including the titles and abstracts obtained through the search was split in four. The reviewers independently screened two of the subdatabases each so that each title/abstract was screened in duplicate. Studies were included in the second screening round if selected by at least one reviewer. The second selection round comprised screening of the full-text articles. Two authors (FZ and AU) independently screened all articles for eligibility using the aforementioned criteria. Any discrepancies were resolved by discussion until consensus was reached, and unresolved discrepancies were arbitrated by a third reviewer (MP).

Data extraction and validity checking

Data regarding program characteristics and program outcomes (see Box 2) were extracted and cross-checked by two reviewers (FZ and AU). We distinguished two types of settings and presented the screening programs according to these: integrated and nonintegrated screening. Integrated screening refers to programs that are integrated within already existing health care facilities, whereas in nonintegrated screening, the program is exclusively set up for the screening. In addition, since screening strategies may differ according to the prevalence of HCV infection in a specific country, data are presented not only by the type of setting, but also separately for low prevalence (≤2% according to the Centers for Disease Control and Prevention [CDC] (1)) and intermediate to high prevalence countries for HCV infection.

Box 2: Parameters of screening programs

Program characteristics

- Country (and region, if applicable) of the study
- Estimated prevalence of HCV antibody in the country
- Calendar year(s) of data collection
- Duration of enrolment/screening period
- Setting (i.e., whether screening for HCV infection was integrated within already existing health care facilities or whether the program was exclusively set up for the screening [i.e., nonintegrated screening])
- Use of psychosocial theory or previous research findings as a basis for communicating the screening and for stimulating screening uptake
- Size of the targeted population
- Use of media activities and/or personal invitations to promote screening
- Use of screening criteria based on risk factors for HCV infection
- Incentive or participant's costs for screening
- Anonymous or nonanonymous participation
- Type of HCV test(s) that was used for screening [a]
- Screening for other diseases performed
- Use of a comparison group for evaluation purposes

Program outcomes

- Response rate (i.e., proportion of the target population that was screened)
- Number of participants (i.e., number of individuals that were screened)
- Number of HCV-infected cases identified
- Number of HCV-infected cases already known
- HCV-antibody prevalence [b]
- Risk profile of identified cases
- Proportion of HCV-antibody positives with detectable HCV RNA
- Number of referrals to specialist
- Start and outcomes of treatment

[a] Since the introduction of the first HCV antibody test in 1991, several improvements have been made in HCV diagnostics. Anti-HCV and HCV-RNA prevalence rates of studies were considered suboptimal 1) if data was collected prior to 1994 when sensitivity and specificity of tests were not optimal (18, 30)) or 2) if studies did not confirm reactive HCV antibody test results by immunoblot or PCR to eliminate false positives. Tests were considered valid if performed after 1993 and if 1) second- or higher- generation immunoblot assays from Ortho, Chiron, Novartis (RIBA), Innogenetics (LiaTek), Pasteur (DECISCAN HCV), Genelabs Diagnostics (HCV BLOT), or Mikrogen (recomBlot HCV IgG 2.0) were used to confirm HCV antibody reactive results or 2) PCR was used to confirm HCV-antibody reactive results. The validity of outcomes of studies that did not indicate which test was used, and studies that used dried blood spot (DBS), oral fluid screening, or immunoblot assays different from those indicated above, was considered undecided.

[b] If the study reported HCV prevalence, but without specifying whether it concerned HCV-antibody or HCV-RNA prevalence, and if information about the test that was used was lacking, we assumed

it to be HCV-antibody prevalence.

Results

The search strategy identified 5,263 records from the MEDLINE database and 6,300 from the EMBASE database. After duplicates were eliminated, 7,052 of 11,563 records remained (see Figure 1). Of those, 737 were selected as potentially relevant to the review, and full-text articles were retrieved and reviewed independently in duplicate. We excluded 677 articles; 652 articles because they did not meet the inclusion criteria (the majority because they were prevalence studies, or studies that only reported statements about screening guidelines and policy, not including any screening results), and 3 Japanese articles and 1 Italian because they did not provide an English abstract. In addition, 20 articles (two Chinese (31;32), eight Japanese (33-40), one Icelandic (41), four Russian (42-45), two Turkish (46;47), one Czech (48), and two Taiwanese (49;50)) seemed relevant on the basis of the English abstracts, but were excluded as the abstracts alone did not yield enough information for review. One article was excluded because the same data were reported in two papers (51;52). Of the 60 studies remaining, references lists were screened yielding an additional 106 potentially relevant records. The full-text articles were retrieved and screened independently in duplicate, and 7 of the 106 studies were selected for inclusion. In total, 67 studies remained in the final selection.

The 67 studies identified were done in the USA (n=27), Europe (n=27; mostly France and the United Kingdom [UK]), Asia (n=4), Australia (n=4), South America (n=3), Egypt (n=1) and Saudi Arabia (n=1). We identified 24 nonintegrated and 41 integrated studies, plus two studies that used both strategies (the latter are shown in Table 1a for the results of the nonintegrated part of their program, and in Table 2b for the results of the integrated part of their program) (53;54). A total of 85% (22/26) of the nonintegrated programs and all of the integrated programs were from low prevalence

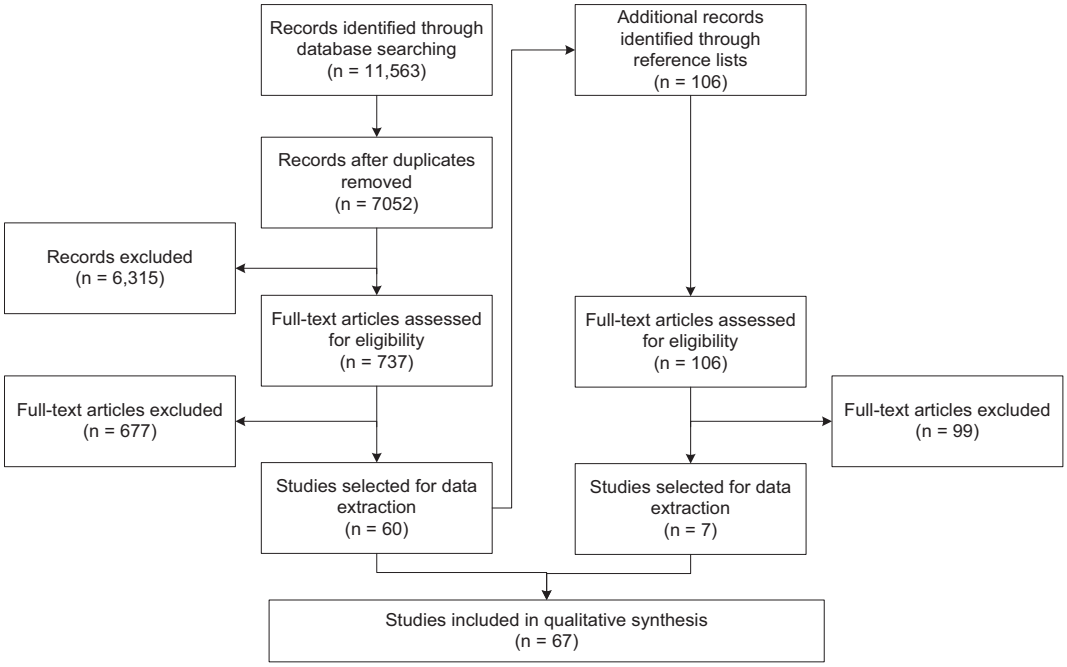

Figure 1. Overview of search strategy, data collection, and data review and extraction processes

Nonintegrated hepatitis C screening programs in countries with low prevalence rate of HCV infection (n=22)

Program characteristics: Table 1a presents the 20 nonintegrated screening programs for HCV infection and the 2 programs that combined an integrated and non-integrated screening approach that were performed in countries with low prevalence rate of HCV infection. In total, 12 of the 22 programs were carried out in the USA. The table is sorted by population type; seven studies were aimed at screening the general population; the other 15 studies targeted specific groups in which a higher prevalence of HCV infection might have been expected (e.g., migrants, homeless individuals, firefighters, surgeons). Five of the 22 programs reported the use of personal screening invitations either face to face or by mail, and 12 reported the use of media activities to attract individuals for screening. None of the programs reported the use of psychosocial theory or knowledge about determinants facilitating participation in screening programs. Eight studies reported the possibility for individuals to participate anonymously. Only nine of 22 studies reported the costs for participants to be screened; in all of them, screening was offered free of cost, and one study offered a t-shirt as an incentive for screening (73).

With respect to screening procedures, except for two, all programs used venipuncture to collect serum. A program targeted at firefighters (69) used home specimen collection kits for serum collection. A program targeted at migrants (54) initially used oral fluid anti-HCV antibody tests followed by a blood test for those who tested positive (no further details reported). In the majority (16/22) of the programs, participants were also screened for other infections (mostly HIV and hepatitis B virus [HBV] infection) or liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST]).

Program outcomes: In total, the 22 programs screened about 32,000 individuals for anti-HCV antibodies (range: 19-8,650) and identified 1,809 HCV-infected individuals (range: 0-604). The screening uptake was reported in 13/22 studies, and varied from >20% in a screening program at a local health fair in the USA (62) to 100% in a program that used household visits to identify transfusion recipients and invite them for screening in Cuba (60). The prevalence of HCV infection varied from 0% to 28.3%. The latter was found in a community-based screening program in New York City targeted at migrants from the former Sovjet Union. Risk-profile data for HCV infection were available for only a subset of the HCV-infected individuals in that study and included intramuscular injections and blood transfusions. Some of the programs among a so-called 'general population' (see Table 1a, row 1-7) that found relatively high prevalence rates of HCV infection (e.g., 10.5% in a walk-in clinic (56)), did not collect risk profile data of their participants, limiting the interpretability of their findings. Two of 22 studies used a prescreening risk assessment in order to limit screening to those with established risk factors for HCV infection: one did not report the prevalence rate nor screening uptake (58); the study in Cuba reported the highest screening uptake (100%) and found relatively high prevalence rate of HCV infection (8.6%), but absolute numbers were small.

Four of the 22 programs screened primarily people from Asia, either through screening programs in Asia (Japan), or programs in Western countries targeting Asian migrants. In all but one of these programs, relatively high prevalence rates of HCV infection were found, varying from 5.2% to 19.7%. In contrast, the programs targeting those with occupational risk for HCV infection (n=7) found relatively low prevalence rates (all <1.1%, except for 3.6% among firefighters and 5.3% among health care workers involved with liver transplantations).

We did not notice clear differences in screening uptake or prevalence of HCV infection related to the use of personal invitations for screening, the use of media to attract individuals for screening, and whether or not individuals were screened for other infections as well. In general, a lower prevalence rate of HCV infection was found in the studies (n=8) that provided anonymous screening; however, most of these studies (6/8) targeted those with occupational risk, explaining the lower prevalence.

Only one study compared the results of their outreach screening program with data collected in the same period at a screening clinic that is visited by individuals on their own initiative (72). A higher prevalence rate of HCV infection was found during outreach screening (4.9% versus 1.6%, respectively). However, the number of individuals that returned to obtain their test results was much lower for the outreach approach (65.8% versus 91.8%, respectively).

Six of the 22 studies reported the proportion of viremic patients, which varied from 50% to 96.5%. Only one study reported the proportion of identified chronic hepatitis C (CHC)-infected individuals that started treatment (37%) (58), but did not report how many of those reached a sustained virological response (SVR).

Nonintegrated hepatitis C screening programs in countries with intermediate to high prevalence rate of HCV infection (n=4)

Program characteristics: Table 1b presents the four nonintegrated screening programs for HCV infection that were performed in countries with intermediate to high prevalence of HCV infection (Taiwan [n=2], Pakistan [n=1] and Egypt [n=1]). All studies targeted the general population; one targeted children less than 16 years of age. A study from Egypt reported household visits to personally invite individuals for screening (75); the study among children reported personal invitations (method not specified) (78). All except the study among children reported the use of media activities to attract individuals for screening. None of the programs reported the use of psychosocial theory or knowledge about determinants facilitating participation in screening programs. A risk-based screening selection was used in the program in Egypt, where screening was limited to those with symptoms and ALT levels $\geq$ 2 times the upper limit of normal. None of the studies reported the possibility for individuals to participate anonymously. Two studies reported about the costs for participants to be screened; one of them offered screening free of cost, whereas the other program (77) offered screening at 20% of the market value. None of the studies used a comparison group for evaluation purposes. With respect to screening procedures, all four studies used venipuncture for specimen collection. A study from Pakistan (77) used a rapid anti-HCV antibody test. In most (3/4) studies, participants were also screened for other infections (mostly HBV) but not for HIV.

Program outcomes: In total, the four programs screened 161,341 individuals for anti-HCV antibodies (range: 47-157,720) and identified 7,488 HCV-infected individuals (range: 11-6,904). The screening uptake was reported in two studies; it was very low (<1%) in a city screening program in Pakistan, and very high (93.6%) in a screening program in kindergartens and schools in Taiwan. Although the screening uptake in the latter was high, the prevalence was low (0.9%). The prevalence rates of HCV infection in the other programs varied from 4.4% in a community-based screening program in Taiwan up to 78.8% in a program in Egypt that limited screening to those with symptoms and increased ALT levels (75). Two of the four studies reported the proportion of viremic patients, which was relatively low (27.3%) in the study among children, and 70.2% in the Egyptian study. None of the studies reported the proportion of CHC-infected patients that started treatment and/or reached

SVR.

Integrated hepatitis C screening programs in countries with low prevalence rate of HCV infection (n=41)

We identified 41 screening programs for HCV infection in the following clinics that offer care not related to liver disease: sexually transmittable diseases (STD) clinics (n=11); GP clinics (n=10, including two programs that also used a nonintegrated approach); Veterans Affairs (VA) health centers (n=5); antenatal/obstetric/fertility clinics (n=5); clinics for psychiatric patients (n=3); and other clinics or services (n=7). Tables 2a-f present the programs separately for each type of setting. All programs were carried out in countries with low prevalence rate of HCV infection.

STD clinics (n=11)

Program characteristics: The majority (7/11) of the screening programs for HCV infection in STD clinics were carried out in the USA. None of the studies reported the use of personal invitations or media to promote screening for HCV infection inside or outside the clinic. In five of the 11 programs, screening was limited to high-risk groups for HCV infection, varying from single groups (e.g., those with a history of IDU (84), or MSM (80)) to individuals from multiple risk groups, such as those who have had body piercing or tattooing in unsanitary conditions, transfusion recipients before 1987, or those who have had a needlestick injury (79). None of the studies reported the use of psychosocial theory or knowledge about determinants facilitating participation in screening programs, and none reported whether or not individuals were charged for screening, or whether anonymous participation in the screening program was possible. None of the programs used a comparison group for evaluation purposes. All programs used venipuncture for specimen collection.

Program outcomes: In total, at the STD clinics, the 11 programs screened 150,233 individuals for anti-HCV antibodies (range: 618-90,424) and identified 13,397 HCV-infected individuals (range: 8-8,964). Six of the 11 programs reported the screening uptake, which varied from 14.0% to 95.8%. The prevalence rates of HCV infection varied from 0.1% to 28.0%. Only one study reported that an opt-out strategy was used, but did not report the screening uptake (88). Of the five studies that limited screening to risk groups for HCV infection, four reported a high prevalence rate (>15%). In contrast, the prevalence rates in the six studies without a risk selection varied from 0.1% to 4.9%. In all programs at the STD clinics, a history of IDU was found in the risk profile of the identified HCV-infected individuals, or was found associated with HCV infection.

Only three of the 11 programs reported the proportion of viremic patients, varying from 61.7% to 69.3%. None of the studies reported the proportion of HCV-infected patients that started treatment and/or reached SVR.

GP clinics (n=12)

Program characteristics: The majority (8/12) of the screening programs for HCV infection in GP clinics were carried out in France. In most programs (9/12), screening was limited to risk groups for HCV infection within the GP-patient population (specific migrant groups (53;54); risk groups such as those with a history of IDU and recipients of blood transfusions before 1991 (90;92;93;95-98)). One program was carried out in a health care center that attracted people with poor access to health care, mostly migrants (52), and one was carried out in an area of low socioeconomic status (91). In two of the 12 programs, individuals who were in the GP's waiting room were approached and invited for screening (52;54), and five programs used media activities to attract individuals for screening.

None of the programs reported the use of psychosocial theory or knowledge about determinants facilitating participation in screening programs. Of the 12 studies, four reported that screening was free of cost (90;93;98;119), whereas the others did not report participants' costs for screening. Only the screening program among people with poor access to health care offered the possibility of anonymous screening (52).

In reference to screening procedures, all but two studies used venipuncture for specimen collection. Two studies used oral fluid anti-HCV antibody tests, followed by blood tests for those who tested positive. The majority (9/12) of the programs focused solely on HCV infection. The three programs that screened predominantly migrants also included screening for HBV infection (52-54).

Program outcomes: In total, the 12 programs screened 30,022 individuals for anti-HCV antibodies (range: 117-15,952) and identified 522 HCV-infected individuals (range: 0-276). Six of the 12 programs reported the screening uptake, which varied from 27.8% to 82.5%. The prevalence of HCV infection varied from 0% to 30.8%. Only one study reported an opt-out strategy, with a screening uptake of 59% (94). Of the 12 programs, three primarily screened migrants (prevalence rates 0%, 1.2% and 5.8%), seven used risk factors other than being a migrant as criteria for screening (prevalence rates 1.4% to 30.8%), and one was performed in an area of low socioeconomic status (prevalence rate 12.8%). In contrast, one program that did not use risk factors as screening criteria, and was not performed in an area of low socioeconomic status, found a relatively low prevalence of 0.4% (94). We did not notice clear differences in screening uptake or prevalence related to the use of media to attract individuals for screening. Further, we could not assess whether personally inviting individuals for screening or screening for more than just HCV infection could have influenced the screening uptake, since these studies did not report the screening uptake (52;54).

Four studies checked the results of their screening program against data collected in the same period in comparison clinics or data collected prior to the screening program. A study from the Netherlands concluded that the addition of primary care practice support (e.g. plenary courses for GPs regarding screening for HCV infection) leads to improvements in medical consciousness regarding HCV infection in primary care, which is likely to have a positive effect on case finding (that effect, however, could not be indisputably demonstrated) (96). A study from France concluded that information and training that is adapted to GPs' medical practice can lead to more active involvement of GPs in screening for HCV infection (97). During the intervention the number of GPs that prescribed tests increased, and more HCV-infected patients were detected compared with the year before. Another study from France compared two interventions in the GP clinic; GPs in intervention 1 prescribed HCV testing if risk factors for HCV infection were identified during questioning of patients, whereas GPs in intervention 2 placed posters and leaflets on risk factors in their waiting rooms to motivate patients at risk to discuss screening (98). The numbers of tests prescribed by GPs was relatively low in both interventions, and outcomes of the two interventions with regard to the number of tests and the prevalence were comparable. In a study from Scotland showed that offered screening to all GP visitors aged 30-54 years, 117 individuals were screened for HCV infection (prevalence: 12.8%, 15/117), whereas in a comparison clinic, where no intervention for screening was introduced, no individuals were screened for HCV infection (91).

Only three of the 12 programs in which anti-HCV-antibody positive individuals were identified reported the proportion of viremic patients, varying from 73.3% to 86.4%. Two of these programs reported the proportion who started treatment (18% and 38%), but only one of these two programs

reported the proportion of treated individuals (n=2) who reached SVR (50%, n=1)(91).

Veterans Affairs clinics (n=5)

Program characteristics: All five screening programs for HCV infection in VA clinics were carried out in the USA. No personal invitations or media activities were reported. All screening programs limited the screening to risk groups within the veteran population. In one program, screening was limited to veterans who were admitted for an alcohol and noninjecting drug rehabilitation program (102), while other programs used an extensive list of risk factors, including history of drug use, blood transfusion prior to 1992, and Vietnam veteran. None of the programs reported an opt-out strategy, and none reported the use of psychosocial theory or knowledge about determinants facilitating participation in screening programs, whether or not individuals could participate anonymously, participants' costs for screening, or a comparison group for evaluation purposes. All programs used venipuncture for specimen collection and screened solely for HCV infection.

Program outcomes: In total, the five programs screened 31,483 individuals for anti-HCV antibodies (range: 338-12,485) and identified 1,810 HCV-infected individuals (range: 78-681), although in one program (100) a large number of individuals were already aware of their infection (n=152). The screening uptake was described in three of the five programs, varying from 41.9% to 99.4%. The prevalence of HCV infection in most programs was around 5%, but the program among veterans who were admitted to an alcohol and noninjecting drug rehabilitation program was substantially higher (23.1%). Three programs reported the proportion of viremic patients, varying from 47% to 97.4%. The proportion of patients that started treatment was described in three studies and varied from 15% to 38%. Four studies reported the SVR rate among those who started treatment, ranging from 33% to 47%.

Antenatal/obstetric/fertility clinics (n=5)

Program characteristics: Of the five programs, three were carried out in the UK, one in the USA and one in Brazil. The programs targeted pregnant women, except for a British study in a fertility clinic that was targeted at couples. Media activities to promote the screening programs were described in only one of the five studies; this study used information leaflets to inform women about the screening program, and a personal invitation for participation by the midwife (107). None of the programs reported an opt-out strategy, and none used a risk assessment strategy to limit screening to those at risk, and none reported the use of psychosocial theory or knowledge about determinants facilitating participation in screening programs. The programs did not report the possibility to screen anonymously, or a comparison group for evaluation purposes. The one program reporting screening costs was free of cost to participants (108).

With respect to screening procedures, all but one study used venipuncture for specimen collection. One study used DBS for anti-HCV screening and a second generation ELISA followed by HCV RNA testing using venous blood for confirmation (108). In all but one program, participants were also screened for other infections (mainly HIV and HBV) or liver enzymes (ALT/AST).

Program outcomes: In total, the five programs screened 67,729 individuals for anti-HCV antibodies (range: 1,658-31,081) and identified 283 HCV-infected individuals (range: 9-115). In the two studies reporting screening uptake, rates were very high (≥98%).

In all but one program, the prevalence rates were low, varying from 0.2% to 0.8%. In women at risk for perinatal complications, prevalence was 4.6% (106). In two studies, the proportion of viremic patients was reported, varying from 71% to 73%. In one of the five programs, results of the clinical follow-up and treatment were reported, showing that 67.9% of those identified with CHC started

treatment after delivery, and 80% of those who completed treatment achieved SVR (104).

Psychiatric clinics (n=3)

Program characteristics: Of the three screening programs for HCV infection in psychiatric clinics, two were carried out in Australia, and one in the USA. One program aimed to evaluate whether screening by risk factors would be effective, and limited the screening program in one unit to those with a history of IDU and those exposed to contaminated blood products, whereas in the other unit all patients were screened (110). In the other two programs, no risk selection was used for participation in the screening program. One program promoted screening by using media (111). None of the programs reported an opt-out strategy. The programs did not offer the possibility to screen anonymously, and did not report about participants' costs for screening. Concerning screening procedures, all studies used venipuncture for specimen collection, and all studies exclusively screened for HCV infection.

Program outcomes: In total, the three programs screened 300 individuals (range: 36-98), and identified 40 HCV-infected individuals (range: 3-15). All programs reported the screening uptake, varying from 20.5% to 100%. The prevalence rates of HCV infection varied from 3.2% in the unit without pre-screening risk selection (110), to 41.7% in the unit where screening was limited to those who reported a history of IDU or exposure to contaminated blood products. Noninjecting drug use and history of IDU were reported as the main risk factors among the identified cases. All three programs referred the HCV-infected individuals to a specialist, but only one study (109) reported the outcomes of referral, namely that 50% of patients were viremic, and none had started treatment after two years of follow-up. Of interest, in two programs (110;111), post-test counseling addressing various topics (e.g., education about the illness, risk behavior, safe injection practices, secondary prevention) was also offered to those who reported risk factors but tested HCV negative.

One of the three studies reported that their program was based on psychosocial theory or knowledge about determinants facilitating participation in screening programs for HCV infection. This program promoted screening by using leaflets outlining HCV infection, its risk factors, and the importance of screening, and used individually tailored pre- and post-test counseling that was adapted to individual knowledge and cultural understandings where appropriate (111). Although the uptake of screening in that study was relatively low (20.5%), the prevalence was relatively high (19.7%), especially considering the fact that no prescreening risk selection was used.

Other clinics (n=7)

Program characteristics: In total, seven screening programs for HCV infection were integrated in other clinics or services. These programs varied widely, from screening patients at an emergency health unit in France (112) to screening couples that wish to get married in Saudi Arabia (113). Two programs targeted MSM; one in an outreach service for HIV point-of-care testing in the UK (115), and another in a community care facility in the USA (116). The study in the USA reported the use of media activities to attract participants, wherein MSM were recruited through advertisements as well as by referral of medical staff (116). Two of the seven studies used a prescreening selection; a program at an emergency health unit only screened those with a reported risk factor (112), and in France, only those with elevated ALT levels as determined during routine medical check-up were screened for HCV (112). None of the programs reported the use of psychosocial theory or knowledge about determinants facilitating participation in screening programs, and none reported about the possibility of anonymous screening, or a comparison group for evaluation purposes. The one study reporting about participants' costs for screening mentioned that it was free (116). With respect to screening procedures, all studies used venipuncture for specimen collection. Four of the

seven programs also screened for other diseases (mainly HBV infection).
Program outcomes: In total, the seven programs screened 78,377 individuals (range: 55-74,662), and identified 397 HCV-infected individuals (range: 1-250). The screening uptake was reported in three out of seven programs, varying from 66.2% to 77.6%. The prevalence of HCV infection varied from 0.3% in a mandatory premarital screening program in Saudi Arabia (113) to 11.5% in a program for MSM (116). None of the programs reported an opt-out strategy, and one reported that screening was mandatory but did not report the screening uptake (113). Only three studies reported the proportion of viremic patients, varying from 50% to 73%. Only one study reported the number of patients that started treatment, which was zero (112).

Discussion

This systematic review describes characteristics and outcomes of screening programs for HCV infection in the general population, and includes 67 programs. In total, 24 of them were exclusively set up, whereas 41 were integrated in already existing health care facilities (not aimed at risk groups for HCV infection), and two programs used both an integrated and nonintegrated approach. We identified only four screening programs in countries of intermediate to high prevalence of HCV infection, and all were nonintegrated screening programs. Altogether, the programs that were published identified only approximately 25,700 HCV-infected individuals, a tip of the iceberg considering that HCV infection affects an estimated 130-170 million individuals worldwide (120), of which the majority is considered to be undiagnosed. Clearly, more-effective, large-scale, and structural screening and referral programs are needed to address the HCV-related burden of disease in an era of potent therapy for HCV infection.

The programs were highly heterogenic in their organization, recruitment, and screening procedure, and the vast majority did not use a comparison group to assess the effectiveness of their screening program. Hence, we cannot draw firm conclusions as to which screening program strategy, or which program characteristic (e.g., free-of-cost vs. low-cost screening, anonymous vs. nonanonymous screening, use of particular media to promote screening, opt-in vs. opt-out screening) is more effective than another in attracting or motivating individuals for screening or in attracting those at higher risk for HCV infection. Screening programs that compare different recruitment and screening strategies are needed to gain insight into effectiveness of strategies and program characteristics.

In addition, many studies did not report program characteristics (e.g., the laboratory tests that were used). The same was true for screening uptake and follow-up data, and even if reported, there was not much consistency (e.g., some reported the SVR rate among those who completed treatment, whereas others reported that treatment was ‘rather successful’). The underreporting and the lack of uniformity of data reporting greatly hinder the comparison of screening programs. Data reporting standards (see parameters in Box 2) are needed to be able to compare screening program characteristics and outcomes in order to find out which factors are effective.
With respect to publication bias, programs that were successful in identifying HCV-infected individuals may have been more likely to be published. However, we did identify several programs in which none individuals were diagnosed (54;70). Furthermore, as identification of HCV-infected individuals serves a clinical goal and not necessarily a scientific goal, not all screening efforts have been evaluated or published. Our search identified several announcements of screening activities for HCV infection (e.g., 121-126) or cost-effectiveness evaluations of screening activities (127) that did not provide any further information about the screening program and/or outcomes. Therefore, there

may be more screening programs for HCV infection than those described in this review.
In general, we noticed relatively high prevalence rates in programs that used a prescreening selection based on risk factors for HCV infection (especially in programs that used elevated ALT or a history of IDU as indications for screening for HCV infection) or migrant status, in programs that were carried out in countries or regions of intermediate to high prevalence of HCV infection, and in programs in psychiatric clinics. Also, relatively high prevalence rates were found in nonintegrated programs in low-prevalence countries that targeted the general population (see row 1-7 of Table 1a), even without a prescreening risk assessment. These programs screened a self-referred population, and may have attracted those at risk of HCV infection in the general population (e.g., those with a history of IDU), and therefore observed prevalence rates are higher than those in the general population. For the study by Hayashi et al (61), screening was performed in a specific region in Japan with a presumably high prevalence of HCV infection, explaining the very high prevalence that was found. In most studies, a history of IDU was the main risk factor among the identified HCV-infected individuals. In general, low prevalence rates were found in programs that targeted health care workers, and in programs that were carried out in antenatal clinics. Programs in STD and GP clinics that did not use a prescreening risk selection also found relatively low prevalence rates.

Only one study reported that the promotion of the screening program was based on theoretical insights or knowledge about determinants facilitating participation in screening programs. None of the studies reported the use of simple tools that may increase the screening uptake, such as reminder messages (128;129), or support with planning of when and how to get screened (i.e., creating implementation intentions (130)). In many studies, and especially those describing nonintegrated programs, the uptake of screening was not reported. Only a few studies reported that individuals could be screened anonymously; in the nonintegrated programs, only those targeted at health care workers organized the screening in a way that people could stay anonymous. The fact that HCV infection might be associated with drug use may pose a barrier for individuals and health care providers when deciding for or against screening. Hence, anonymous screening may increase screening uptake, especially among those at high risk of infection.

Surprisingly, none of the programs reported the use of the Internet to attract or inform individuals about screening (data not reported). Even programs that were carried out in recent years when Internet use in high-income countries was widespread did not report the use of this medium. Since Internet use in most high-income countries is relatively common, and the Internet is a relatively anonymous medium, it may fit into screening programs for HCV infection very well. Two programs that were from 2011 and 2012, and therefore not included in this review, used an Internet-based hepatitis C risk-assessment questionnaire and an Internet referral service for blood testing for those at risk of HCV infection (131;132). These programs concluded that such a Web-based and anonymous questionnaire might be useful to detect undiagnosed HCV infections.

We found that integrated screening programs in general screened a larger number of individuals than did nonintegrated screening programs in countries of low prevalence of HCV infection. Integrated screening programs have three advantages in that they do not have to attract their target population for screening, and they can use a facility that is familiar to the public. In addition, they can facilitate continuous screening and follow-up of individuals at relatively low cost, whereas nonintegrated programs offer screening usually for a limited period. On the other hand, integrated screening programs only reach those who have a reason to visit such facilities (unless media campaigns have been used to attract more people), whereas nonintegrated programs may attract a

different risk population that otherwise would not be screened and do not perceive themselves at risk for HCV infection (i.e., the hidden population). We believe that both approaches are useful and complementary. In addition, since nonintegrated screening in general is more complex to organize, it may be efficient to screen for other diseases (e.g., HBV infection) simultaneously, when risk groups overlap (e.g., in migrant populations).

We identified several studies that did not confirm anti-HCV antibody test results. Many of the identified programs targeted asymptomatic individuals in the general population with a relatively low prevalence. In such populations, unconfirmed anti-HCV antibody test results may include 35% (range: 15%–60%) false-positive test results (133). Hence, the program outcomes that are reported may include a substantial degree of uncertainty, and should be interpreted with care. We like to emphasize that screening programs for HCV infection should use screening methods that are in line with recommendations for confirmation testing of all anti-HCV screening-test positive results (133), and describe the tests that were used when publishing the results of their screening projects.

Our review describes several screening programs, but it cannot determine the efficiency and effectiveness of these screening programs in preventing future HCV-related morbidity and mortality. Measuring these effects of screening programs for HCV infection is a challenge because randomized, controlled trials or comparison groups and decades of follow-up time are required. As an alternative method, mathematical modelling studies might be useful. In addition, the efficiency and effectiveness of screening depends not only on the number of individuals screened and the number of individuals identified, but also on the uptake and outcomes of therapy and other preventive measures (e.g., lowering alcohol intake) that may follow from diagnosis. Efficiency relates to the number needed to be screened to identify a treatable case of HCV infection. Surprisingly, most studies did not report such data, and merely mentioned that HCV-infected individuals were notified of their test result and referred for clinical care. Following Wilson and Jungners third screening principle (134), facilities for diagnosis and treatment should be available. This means that the screening program itself is as important as the efforts that are undertaken to bring identified patients into care and have them benefit from preventive measures and/or treatment. Hence, evaluation reports of screening programs should include clinical follow-up and systematically report outcomes.

A recent systematic review by Jones et al. on the effectiveness and cost-effectiveness of interventions aimed at raising awareness of and/or increasing engagement in case finding and testing with high-risk groups for HCV and HBV infection and practitioners included only programs with a comparison group (e.g., randomized controlled trials, pre- and postintervention data, repeated cross-sectional studies) (135). About half of the studies (12/25) included in that review were aimed at high-risk groups for HCV infection that are relatively easy to target, such as current IDU and incarcerated individuals, whereas our review includes studies that aimed to identify the hidden population of HCV-infected individuals. Jones et al. identified drug services and primary care as settings in which interventions could effectively increase screening uptake. They also found that DBS testing in addition to venipuncture might increase screening uptake in drugs services or prisons. In our review, a few studies reported the use of home collection tests, DBS, or oral fluid tests, but these studies did not demonstrate high screening uptake. Further insight into the effect of alternative noninvasive testing procedures on screening uptake is needed. As in our review, Jones et al. concluded that improvement of health outcomes following diagnosis for those identified with CHC deserves careful attention.

In conclusion, HCV infection has serious health implications and, at the start of the era of potent

therapy for CHC, screening programs are not yet reaching all potentially infected individuals worldwide. Therefore more effective programs are urgently needed. This review identified 67 screening programs that targeted risk groups for HCV infection that are hidden in the general population. Relatively high prevalence rates of HCV infection were found in programs that used a prescreening selection based on a risk profile or migrant status, in programs that were carried out in intermediate to high prevalence countries or regions, and in programs in psychiatric clinics. In general, low prevalence rates were found in programs that targeted health care workers and pregnant women. The reported use of motivational communication based on theory and/or determinants facilitating screening, and tools to increase screening uptake were virtually absent. Comparison of the screening programs was strongly hindered by the lack of reported data on screening uptake, program characteristics, the type of diagnostic tests used, and clinical outcomes. In addition, only a few programs used a comparison group to evaluate program effectiveness.

We suggest that screening programs should be theory-based and provide tools to increase screening uptake. For populations with low prevalence of HCV infection, the use of prescreening selection criteria should be considered to increase efficiency. In addition, to be able to assess screening program effectiveness, programs using a comparison group are needed. To improve comparability of screening programs and outcomes, it is necessary for all programs to systematically report program characteristics, screening uptake, the type of diagnostic tests that were used, as well as clinical outcomes.

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Table 1a. Nonintegrated screening programs in low HCV-prevalence countries (≤2%)

Program characteristics									Program outcomes		
First author, year of publication	**Calendar year of data collection**	**Population**	**Country and HCV prevalence according to CDC (1)**	**Setting of screening**	**Duration of screening program**	**Other tests**	**Prescreening selection**	**Media activities**	**Screening uptake and anti-HCV prevalence (95% CI)**	**Risk profile of identified HCV cases / Risk factors associated with HCV**	**Follow-up of HCV-infected individuals**
Kaur, S, 1996 (55)	1992	General population	USA (1.9%): throughout the country	Mainly urban hospital centres	4 days	HBV, ALT	No	Yes	Scr. uptake: appr. 90% Prevalence: 7.0% (604/8650; 95% CI: 6.5-7.5) *	Multivariable regr. analysis - History of IDU - Hemodialysis - Sex with IDU - Blood transfusion - Male gender - Non-white/non-Hispanic - Not vaccinated for HBV	Patients were referred to their physicians for further follow-up. Of 604 anti-HCV positives, 380 (62.9%) had elevated ALT levels. No results were reported. Outcomes: RNA rate: NR Start treatment: NR SVR: NR
D'Souza, RFC, 2004 (56)	2003	General population	UK (1.1%): London	Walk-in clinic at the minor injuries unit at hospital	4 days	Liver function tests	No	Yes	Scr. uptake: NR Prevalence: 10.5% (2/19;95% CI:2.9-31.4) **	NR	Patients were informed in person of the test results. No further follow-up data reported. Outcomes: RNA rate: NR Start treatment: NR SVR: NR
Bellentani, S, 1994 (57)	1994	General population aged 12-65 yrs	Italy (1.1%): Northern Italy, cities Campogalliano and Cormons	Community-based screening	2 years	ALT, AST, gamma-glutamyltranspeptidase, mean cell volume, platelet, erythrocyte and leukocyte counts, HBV	No	Yes	Scr. uptake: 68.1% (6917/10150) Prevalence: 2.9% (199/6917; 95% CI: 2.5-3.3) *	NR	Patients with HCV antibodies underwent additional procedures (e.g., ultrasonography of the liver, liver biopsy when indicated). At the time of the writing, 10% had undergone liver biopsy. No results were reported. Outcomes: RNA rate: NR Start treatment: NR SVR: NR
Trepka, M.J, 2007 (58)	2001- 2003	General population	USA (1.9%): Miami	Hepatitis screening clinic	2.5 year	HBV	Yes, if traditional risk factors apply [b]	NR	Scr. uptake: NR Prevalence: NR (269/NR) ***	Most common risk factor (%) - History of IDU (54.7)	Of the anti-HCV positive clients, 20.8% (56/269) were reached by phone, and 44 were interviewed. Of those, 31 (70.5%) had seen a physician, of which 27 completed their medical evaluation. Of these, 3 completed treatment, 7 were still receiving treatment, 8 had not yet begun treatment, 7 did not need treatment, and 2 were no treatment candidates. Outcomes: RNA rate: NR Start treatment: 37.0% (10/27) SVR: NR

Table 1a cont'd

Program characteristics									Program outcomes		
First author, year of publication	**Calendar year of data collection**	**Population**	**Country and HCV prevalence according to CDC (1)**	**Setting of screening**	**Duration of screening program**	**Other tests**	**Prescreening selection**	**Media activities**	**Screening uptake and anti-HCV prevalence (95% CI)**	**Risk profile of identified HCV cases / Risk factors associated with HCV**	**Follow-up of HCV-infected individuals**
Fagundes, GD, 2008 (59)	2005	General adult urban population	Brazil (1%): Santa Catarina, Criciuma	Public health campaign event	1 day	None	No	Yes	Scr. uptake: NR Prevalence: 2.2% (10/457; 95% CI: 1.2-4.0) *	Univariable regr. analysis: - High number of sex partners	In HCV-RNA positive samples, genotyping was performed for therapeutic reasons. No data about therapy reported. Outcomes: RNA rate: 70.0% (7/10) Start treatment: NR SVR: NR
Jimenez, FP, 2000 (60)	1997-1998	General population 15-70 years	Cuba (1.9%): Havana	House visits of all patients registered at a GP clinic	17 months	None	Yes, history of blood transfusion	No	Scr. uptake: 100% (35/35) Prevalence: 8.6% (3/35; 95% CI: 3.0-22.4) *	NR	All patients were followed and treated at a gastroenterology clinic (results were not reported) Outcomes: RNA rate: NR Start treatment: NR SVR: NR
Hayashi, J, 1995 (61)	1993	General population	Japan (2%): Kyushu Island, Fukuoka Prefecture, 'H Village'	Village screening program	NR	HBV	No	Yes	Scr. uptake: 48.1% (2046/4250) Prevalence: 19.7% (403/2046; 95% CI: 18.0-21.5) *	Most common risk factor (%) - History of blood transfusion (11.9)	NR – the authors write that it is necessary to work out a strategy for the care of the many HCV-infected individuals in this village. Outcomes: RNA rate: 82.9% (334/403) Start treatment: NR SVR: NR
Uddin, G, 2010 (54) [a]	NR	Immigrants from the Indian sub-continent (India, Bangladesh or Pakistan)	UK (1.1%): East London, West London, Walsall, Sandwell, Bradford	Public meetings and testing sessions in community centers (and GP clinic, see Table 2b)	NR	Oral fluid HCV, HBV	No	Yes	Scr. uptake: NR Prevalence: 1.6% (75/4,833; 95% CI:1.2-1.9) at community centers **	Multivariable regr. analysis - Pakistani - Shorter length of stay in the UK - Being tested in East London	Patients were offered an appointment with the local treating physician for confirmation blood testing; 57/75 attended. Outcomes: RNA rate: 96.5% (55/57) Start treatment: NR SVR: NR
Kallman, JB, 2010 (53) [a]	NR	Immigrants from Vietnam	USA (1.9%): Northern Virginia	General health screening at Asian health fairs (and GP clinic, see Table 2b)	NR	HBV	No	NR	Scr. uptake: NR Prevalence: 5.2% (4/77, 95% CI: 2.0-12.6) at health fairs **	Univariable regr. analysis: - Elevated AST	Patients were seen by their primary care givers for further management, or referred for further follow-up and treatment (no results were reported). Outcomes: RNA rate: NR Start treatment: NR SVR: NR

Table 1a cont'd

Program characteristics									Program outcomes		
First author, year of publication	**Calendar year of data collection**	**Population**	**Country and HCV prevalence according to CDC (1)**	**Setting of screening**	**Duration of screening program**	**Other tests**	**Prescreening selection**	**Media activities**	**Screening uptake and anti-HCV prevalence (95% CI)**	**Risk profile of identified HCV cases / Risk factors associated with HCV**	**Follow-up of HCV-infected individuals**
Hwang, JP, 2010 (62)	2006	Asian Americans (predominantly)	USA (1.9%): Houston	Local community health fair	1 day	HBV	No	Yes	Scr. uptake: >20% (202/>1000, of whom 118 Asian Americans) Prevalence: 5.9% (7/118, 95% CI: 2.9-11.7) * Vietnamese: 15.4% other Asian: 1.3%	NR	Of 7 patients, one was lost to follow-up, and 6 were tested for HCV RNA. Those who tested positive were referred to a hepatologist. Access to care was not confirmed, and follow-up data were not reported. Outcomes: RNA rate: 83.3% (5/6) Start treatment: NR SVR: NR
Batash, S, 2008 (63)	NR	Immigrants in NYC from former Sovjet Union	USA (1.9%): NYC	Community based screening	3 days	None	No	Yes	Scr. uptake: NR Prevalence: 28.3% (80/283, 95% CI:23.0-33.5) *	Only available for small subset of cases (97/283) Multivariable regr. analysis: - intramuscular injections - blood transfusions	HCV RNA and ALT testing was only done in the 27 individuals that were identified at screening day 2 and 3. Outcomes: RNA rate: 66.7% (18/27) Start treatment: NR SVR: NR
ARèS 92, 2004 (64)	2004	Guest workers from Africa	France (1.1%): Hauts-de-Seine	Health check in rental apartments for guest workers	3 days	Clinical and dental examination, a chest X-ray and blood tests: fasting glucose, cholesterol, triglycerides, and serologies: HBV, syphilis and HIV	No	Yes	Scr. uptake: 35.6% (110/309) Prevalence: 0.9% (1/110; 95% CI:0.04-5.0) **	NR	For all patients specific management was started (results were not reported). Outcomes: RNA rate: NR Start treatment: NR SVR: NR
Goetz, AM, 1995 (65)	NR	Health care workers (physicians, dentists, nurses and laboratory personnel) with very high, high, and low risk for potential exposure to hepatitis C through the handling of blood and body fluids.	USA (1.9%): Pittsburgh	Two hospitals that do liver transplantations: the Veterans Affairs Medical Center and the Presbyterian University Hospital	NR	None	No	NR	Scr. uptake: NR Prevalence: Overall: 1.2% (3/241; 95% CI: 0.4-3.6) CHCV. **** In HCW involved with liver transplantations: 5.3% (3/57, 95%CI: 1.3-15.5%) versus 0% in the HCW at lower risk.	Univariable regr. analysis: - Working at liver transplant operating room	Clinical evaluation and counseling for those who were not anonymous (results were not reported). Outcomes: RNA rate: - Start treatment: NR SVR: NR

Table 1a cont'd

Program characteristics									Program outcomes		
First author, year of publication	**Calendar year of data collection**	**Population**	**Country and HCV prevalence according to CDC (1)**	**Setting of screening**	**Duration of screening program**	**Other tests**	**Prescreening selection**	**Media activities**	**Screening uptake and anti-HCV prevalence (95% CI)**	**Risk profile of identified HCV cases / Risk factors associated with HCV**	**Follow-up of HCV-infected individuals**
Thomas, DL, 1993 (66)	1991	Health care personnel	USA (1.9%): East Baltimore	Hospital	9 months	HBV	No	Yes	Scr. uptake: >90% Prevalence: 0.7% (7/943; 95% CI: 0.4-1.5) *	Most common risk factor (%) - Blood transfusion (14.3)	Patients were offered consultation (results were not reported). Outcomes: RNA rate: NR Start treatment: NR SVR: NR
Panlilio, AL, 1995 (67)	1992	Surgeons	USA (1.9%): throughout two metropolitan areas	21 hospitals in two metropolitan areas	7 months	HBV, HIV	No	Yes	Scr. uptake: 26.7% (770/2887) Prevalence: 0.9% (7/770; 95% CI: 0.4-1.9) *	None identified	Patients were offered post-test-counseling (results were not reported). Outcomes: RNA rate: NR Start treatment: NR SVR: NR
Upfal, MJ, 2001 (68)	NR	Firefighters, police and EMS	USA (1.9%): Detroit	Survey among firefighters, police, emergency medical service (EMS) personnel	NR	None	No	Yes	Scr. uptake: 42.9% (2447/5700) Prevalence: 1.1% (28/2447; 95% CI: 0.8-1.6) *	Multivariable regr. analysis: - EMS personnel, fire fighters - Guilty about drinking - Surgery<1990 - Older age - Life dissatisfaction	Patients were advised of the need and available resources for follow-up confirmatory testing, counseling, and preventive and medical care (results were not reported). Outcomes: RNA rate: NR Start treatment: NR SVR: NR
Datta, S, 2003 (69)	1999	Active and retired fire fighters from local union	USA (1.9%): Philadelphia	Home testing screening project	NR	None	No	NR	Scr. uptake:48.3% (2127/4400) Prevalence: 3.6% (77/2127, 95% CI: 2.9-4.5%) **	Multivariable regr. analysis: -Blood transfusion before 1992 - History of illegal drug use - Black race	Patients received their results by phone. Outcomes: RNA rate: NR Start treatment: NR SVR: NR
Gershon, RRM, 1995 (70)	NR	Funeral service practitioners	USA (1.9%): Maryland	Testing on appointment	NR	HIV, HBV	No	NR	Scr. uptake: 49.6% (130/262) Prevalence: 0% (0/130; 95% CI:0-2.9) **	Not applicable (none identified)	Not applicable (none identified)
Torda, AJ, 2008 (71)	2002-2005	First-year medical students	Australia (2%): New South Wales	Mandatory vaccination and screening program in a vaccination clinic	4 years	HIV, HBV, measles, mumps, rubella, and varicella-specific IgG antibodies	No	NR	Scr. uptake: 85.0% (733/862) Prevalence: 0.5% (4/733; 95% CI:0.2-1.4) **	NR	Patients were appropriately followed-up (results other than chronicity rate were not reported). Outcomes: RNA rate: 50.0% (2/4) Start treatment: NR SVR: NR

Table 1a cont'd

Program characteristics									Program outcomes		
First author, year of publication	**Calendar year of data collection**	**Population**	**Country and HCV prevalence according to CDC (1)**	**Setting of screening**	**Duration of screening program**	**Other tests**	**Prescreening selection**	**Media activities**	**Screening uptake and anti-HCV prevalence (95% CI)**	**Risk profile of identified HCV cases / Risk factors associated with HCV**	**Follow-up of HCV-infected individuals**
Plard, C, 2007 (72)	2005	Underprivileged people at risk of HIV: IDU, illegals, etc.	France (1.1%): Paris	Outreach screening compared with records of individuals that came to a free and anonymous hospital-based HIV testing clinic	1 year	HIV, HBV, syphilis	No	NR	Scr. uptake outreach: 98.6% (427/433) Prevalence (outreach): 4.9% (21/427; 95% CI:3.2-7.4) Prevalence (clinic): 1.6% (7/427; 95%CI: 0.8-3.3) **	NR	NR Outcomes: RNA rate: NR Start treatment: NR SVR: NR
Boyce, DEC, 2009 (73)	2006	Homeless individuals	USA (1.9%): Hawaii, Oahu	Hepatitis health fair organized in a shelter for homeless people	1 day	HBV	No	NR	Scr. uptake: unclear Prevalence: 7.5% (3/40; 95% CI: 2.6-19.9) **	Most common risk factor (%) - Jail time (100) - History of IDU (67) - Tattoos (67) - Piercings (67) - Snorting drugs (33) - Blood transfusion (33) - Sex partner with HCV infection (33)	Participants were provided with information about available health care resources in the event that they tested positive (results were not reported). Outcomes: RNA rate: NR Start treatment: NR SVR: NR
Arumainayagam J, 2009 (74)	2007	Asymptomatic MSM (and symptomatic MSM who declined referral to the genitourinary medicine clinic)	UK (1.1%): Walsall	Outreach sessions at the sauna	1 year	HBV, HIV, syphilis, chlamydia, gonorrhea	No	NR	Scr. uptake: NR Prevalence: 2.2% CHCV (2/91; 95% CI: 0.60-7.66) **	NR	Patients were referred to and attended their local genitourinary medicine clinic (results were not reported). Outcomes: RNA rate: - Start treatment: NR SVR: NR

Note: CI = confidence interval; NR = not reported; IDU = injecting drug use; HCV = hepatitis C virus; CHCV = chronic hepatitis C virus; HBV = hepatitis B virus; HIV = human immunodeficiency virus; ALT = alanine aminotransferase; AST = aspartate aminotransferase; MSM = men who have sex with men; HCW = health care worker; SVR = sustained virological response; PCR = polymerase chain reaction

* HCV-antibody prevalence is considered suboptimal (data were collected before 1994 when sensitivity/specificity of tests was not optimal, or reactive HCV-antibody test results were not confirmed by immunoblot).
** The reliability of the reported HCV-antibody prevalence is undecided (data were collected after 1993, but the diagnostic tests are unspecified, or other than described below, or dried blood spots or oral fluid samples were used).
*** HCV-antibody prevalence is considered valid; data were collected after 1993, and reactive HCV-antibody test results were confirmed by second or higher generation immunoblot assays from Ortho, Chiron, Novartis (RIBA), Innogenetics (LiaTek), Pasteur (DECISCAN HCV), Genelabs Diagnostics (HCV BLOT), or Mikrogen (recomBlot HCV IgG 2.0).
**** HCV-antibody prevalence is considered valid, but reflecting chronic HCV infection (data were collected after 1993, and reactive HCV antibody test results were confirmed by PCR).

[a] These programs combined a nonintegrated screening approach with integrated screening at the GP clinic (see Table 2b). Here only results of the nonintegrated screening are presented.
[b] History of IDU, receiving blood transfusions or organ transplants prior to July 1992, clotting factor concentrates produced before 1987, being notified to have received HCV-positive blood, ever on chronic hemodialysis, persistently elevated ALT levels, ever exposed to HCV-positive blood through needlestick injuries, born to an HCV-positive woman.

Table 1b. Nonintegrated screening programs in intermediate to high HCV-prevalence countries (>2%)

Program characteristics									Program outcomes		
First author, year of publication	**Calendar year of data collection**	**Population**	**Country and HCV prevalence according to CDC (1)**	**Setting of screening**	**Duration of screening program**	**Other tests**	**Pre-screening selection**	**Media activities**	**Screening uptake and anti-HCV prevalence (95% CI)**	**Risk profile of identified HCV cases / Risk factors associated with HCV**	**Follow-up of HCV-infected individuals**
Meky, FA, 2006 (75)	2002-2005	General population	Egypt (6.6%): Two rural villages in the Nile Delta	Community health clinic and private clinics for acute cases	29 months	HAV, HBV, HEV, CMV, Epstein-Barr	Only those with symptoms and ALT levels =>2 times the upper limit of normal were tested	Yes	Scr. uptake: NR Prevalence: 78.7% (37/47; 95% CI:65.1-88.0 *	NR	At 2 and 6 months following initial examination, follow-up testing was done to confirm or reclassify the diagnosis (i.e., viral clearance or persistent infection). No data was reported about medical follow-up of chronically infected patients. Outcomes: RNA rate: 70.2% (33/37) Start treatment: NR SVR: NR
Chen, C-H, 2007 (76)	1996-2005	General population aged ≥18 yrs	Taiwan (2.1% [a]): throughout the country	Outreach community based screening	10 years	HBV, ALT, AST	No	Yes	Scr. uptake: NR Prevalence: 4.4% (6904/157720; 95% CI: 4.3-4.5) **	NR	Patients were requested to return to the collaborating hospitals for subsequent management (results were not reported). Outcomes: RNA rate: NR Start treatment: NR SVR: NR
Aslam, M, 2001 (77)	2000	General population	Pakistan (6.6%): Lahore and Gujranwala	City screening program	NR	None	No	Yes	Scr. uptake: Lahore: 0.01% 488/5063500 Gujranwala: 0.2% (1922/1124800) Prevalence: Lahore: 16% (78/488; 95% CI:13.0-19.5) Gujranwala: 23.8% (458/1922; 95% CI: 22.0-25.8) *	Listed risk factors: - Blood transfusion - Surgery/dental work - Multiple factors - Mostly other, non-specified risk factors	Patients were informed about the possibility of eradication of the virus, and treatment in its early stages (further data not provided). Outcomes: RNA rate: NR Start treatment: NR SVR: NR

Table 1b cont'd

Program characteristics									Program outcomes		
First author, year of publication	**Calendar year of data collection**	**Population**	**Country and HCV prevalence according to CDC (1)**	**Setting of screening**	**Duration of screening program**	**Other tests**	**Pre-screening selection**	**Media activities**	**Screening uptake and anti-HCV prevalence (95% CI)**	**Risk profile of identified HCV cases / Risk factors associated with HCV**	**Follow-up of HCV-infected individuals**
Lu, SN, 1998 (78)	1994	General population <16 yrs	Taiwan (2.1% [a]): Paisha Township, Penghu Islets	Kindergartens and schools	1 month	HBV	No	NR	Scr. uptake: 93.6% (1164/1243) Prevalence: 0.9% (11/1164; 95% CI: 0.5-1.7) overall * 3-6 yrs: 0% 7-12 yrs: 0.8% 13-15 yrs: 1.9%	Listed risk factors: - Surgery - Intramuscular injection - Intravascular injection - Intravascular infusion	All anti-HCV positive children were followed annually for 2 years with upper abdominal sonography, AST, ALT, anti-HCV and HCV RNA. No data was reported about medical follow-up of chronically infected children. Outcomes: RNA rate: 27.3% (3/11) Start treatment: NR SVR: NR

Note: CI = confidence interval; NR = not reported; IDU = injecting drug use; HCV = hepatitis C virus; HBV = hepatitis B virus; HAV = hepatitis A virus; HEV = hepatitis E virus; CMV = cytomegalovirus; ALT = alanine aminotransferase; AST = aspartate aminotransferase; SVR = sustained virological response

* HCV-antibody prevalence is considered suboptimal (data were collected before 1994 when sensitivity/specificity of tests was not optimal, or reactive HCV-antibody test results were not confirmed by immunoblot).
** The reliability of the reported HCV-antibody prevalence is undecided (data were collected after 1993, but the diagnostic tests are unspecified, or other than described below (see ***), or dried blood spots or oral fluid samples were used).
*** HCV-antibody prevalence is considered valid; data were collected after 1993, and reactive HCV-antibody test results were confirmed by second or higher generation immunoblot assays from Ortho, Chiron, Novartis (RIBA), Innogenetics (LiaTek), Pasteur (DECISCAN HCV), Genelabs Diagnostics (HCV BLOT), or Mikrogen (recomBlot HCV IgG 2.0).

[a] HCV prevalence based on prevalence of country neighbours

Table 2a. Integrated screening programs at clinics for sexually transmitted diseases (STD)

Program characteristics									Program outcomes		
First author, year of publication	Calendar year of data collection	Population	Country and HCV prevalence according to CDC (1)	Setting of screening	Duration of screening program	Other tests	Prescreening selection	Media activities	Screening uptake and anti-HCV prevalence (95% CI)	Risk profile of identified HCV cases / Risk factors associated with HCV	Follow-up of HCV-infected individuals
D'Souza, G, 2003 (79)	2001	STD clinic clients	USA (1.9%): Houston	STD clinic	9 months	STD	Yes, risk assessment questionnaire. screening offered to high-risk groups [a]	NR	Scr. uptake: 95.8% (822/859) Prevalence: 15.3% (126/822; 95% CI:12.7-17.7) *	Multivariable regr. analysis: - History of IDU - Age ≥25 yrs - Heroin use - Non-transfusion/ transplantation blood exposure - Shared straw to snort drugs	Patients were referred to appropriate settings for follow-up (no results were reported). Outcomes: RNA rate: NR Start treatment: NR SVR: NR
Scott, C, 2010 (80)	2007	STD clinic clients	UK (1.1%): London, Chelsea and Westminister hospital	STD clinic in hospital	6 months	STD	Yes, MSM	NR	Scr. uptake: 68.6% (2309/3365) Prevalence: 0.6% (15/2309; 95% CI:0.4-1.1%) **	Listed risk factors: - HIV+ - History of IDU - Unprotected anal intercourse	HCV RNA was tested in 13/15 HCV antibody positive persons. Outcomes: RNA rate: 69.2% (9/13) Start treatment: NR SVR: NR
Weisbord, JS, 2003 (81)	2001	STD clinic clients	USA (1.9%): Miami	STD clinic	3 months	HAV, HBV	No	NR	Scr. uptake: 50.3% (687/1365) Prevalence: 4.7% (32/687; 95% CI: 3.3-6.5) ***	Multivariable regr. analysis: - History of IDU - Sex with HCV+ person - spent ≥ 1 day in prison - Older age	Patients received their test results within two weeks (no further results reported). Outcomes: RNA rate: NR Start treatment: NR SVR: NR
Gunn, RA, 2003 (82)	1999-2000	STD clinic clients	USA (1.9%): San Diego	STD clinic	8 months	STD	No	No	Scr. uptake: NR Prevalence: 4.9% (165/3367; 95% CI: 4.2-5.7) ***	Multivariable regr. analysis: - History of IDU - Age ≥30 yrs - ever in jail - blood transfusion before 1992 - history of bacterial STD - IDU sex partner	Post-test counseling was offered. A list of medical care resources was provided. In total, 136/165 were interviewed of whom 44% had no medical insurance, but 87% planned to have a medical evaluation. Outcomes: RNA rate: NR Start treatment: NR SVR: NR
Mapagu, M, 2008 (83)	2000-2002	STD clinic clients	Australia (2%): Canberra	STD clinic	3 years	STD, BBV	No	NR	Scr. uptake: 46.0% (3113/6774) Prevalence: 3.1% (95/3113; 95% CI: 2.5-3.7%) **	Listed risk factors: - History of IDU - Tatoos - Body piercings - Blood transfusion - IDU partner - Needle stick - Mother HCV+ - Medical treatment overseas in childhood - Prison	Of the 95 HCV antibody positive persons, 47 were tested for HCV RNA. Outcomes: RNA rate: 61.7% (29/47) Start treatment: NR SVR: NR

Table 2a cont'd

Program characteristics									Program outcomes		
First author, year of publication	**Calendar year of data collection**	**Population**	**Country and HCV prevalence according to CDC (1)**	**Setting of screening**	**Duration of screening program**	**Other tests**	**Prescreening selection**	**Media activities**	**Screening uptake and anti-HCV prevalence (95% CI)**	**Risk profile of identified HCV cases / Risk factors associated with HCV**	**Follow-up of HCV-infected individuals**
Zimmerman, R, 2007 (84)	2001-2005	STD clinic clients	USA (1.9%): Illinois excluding Chicago	STD clinics	5 years	HBV (only 2001), STD	Yes: 2001: IDU and snorting drugs were criteria. From 2002: only IDU	NR	Scr. uptake: NR Prevalence: 21.2% (646/3042; 95% CI: 19.8-22.7) ***	Listed risk factors: - Mainly IDU	Because of inadequate resources, the referrals and follow-up were not monitored. Outcomes: RNA rate: NR Start treatment: NR SVR: NR
Subiadur, J, 2007 (85)	2000-2005	STD clinic clients	USA (1.9%): Denver	STD clinics	6 years	STD, HIV	Yes: IDU, HCV-infected sex partner, blood transfusion before 1992	NR	Scr. uptake: NR Prevalence: 28.0%. (467/1666; 95% CI: 25.9-30.2) **	NR	Patients were referred to a specialist but a sub-study of 65/467 clients showed that <20% followed through with recommended services. Outcomes: RNA rate: NR Start treatment: NR SVR: NR
Heseltine, G, 2007 (86)	2000-2005	Not specified; clients of the various settings	USA (1.9%): Texas	Several HIV/STD service providers: HIV counseling and testing sites; drug treatment facilities, corrections facilities, field visit/ outreach sites (e.g., bars, adult bookstores, homeless shelters), STD clinics, family planning clinic, primary health care facility	6 years	STD, HIV	Yes: IDU, sharing equipment used to snort drugs; having received a tattoo or piercing under unsanitary conditions; having 50 or more lifetime sex partners; exchanging sex for money; having sex with an HCV-positive person; people with some medical exposures and occupations	No	Scr. uptake: NR Prevalence: 23.2% (8964/38717; 95% CI: 22.7-23.6) ***	Listed risk factors: - History of IDU (main risk factor) - Risky tattoo/piercing - Risky sex - Blood or medical exposure - Sharing snorting equipment - Occupational exposure	Post-test counseling and referral to public and private providers in the local community was offered. 50.3% of 776 substance abuse referrals, 22.4% of 4410 medical evaluation referrals, and 17.4% of 2299 vaccination referrals were confirmed. Outcomes: RNA rate: NR Start treatment: NR SVR: NR
Gunn, RA, 2001 (87)	1998	STD clinic clients	USA (1.9%): San Diego	STD clinic	6 weeks	HBV	No	No	Scr. uptake: 82.4% (618/750) Prevalence: 3.4% (21/618; 95% CI: 2.2-5.1) **	Listed risk factors: - History of IDU - Among non-IDU: age ≥30 yrs	HCV-positive persons were given information about the prevention of HCV transmission and a list of facilities where they might obtain a medical evaluation. Appr. 8 months after the project, 14/21 clients were contacted of whom 6 had seen a physician for medical evaluation. Outcomes: RNA rate: NR Start treatment: NR SVR: NR

Table 2a cont'd

Program characteristics									Program outcomes		
First author, year of publication	**Calendar year of data collection**	**Population**	**Country and HCV prevalence according to CDC (1)**	**Setting of screening**	**Duration of screening program**	**Other tests**	**Prescreening selection**	**Media activities**	**Screening uptake and anti-HCV prevalence (95% CI)**	**Risk profile of identified HCV cases / Risk factors associated with HCV**	**Follow-up of HCV-infected individuals**
Ellks, R, 2010 (88)	2008	Visitors of sexual and reproductive health service	UK (1.1%): Crewe	STD and reproductive Health Service (integrated service)	1 year	HIV, syphilis, HBV	No	No	Scr. uptake: NR Prevalence: 0.1% (8/5468; 95% CI: 0.1-0.3) **	Listed risk factors: - History of IDU - MSM who snorted drugs - born outside the UK - HIV infection	There were follow-up appointments for those who tested positive. Outcomes: RNA rate: NR Start treatment: NR SVR: NR
Tweed, E, 2010 (89)	2002-2007	Visitors of STD and contraceptio n and sexual health clinics, and specialist HIV services	UK (1.1%): Throughout the country	STD clinics, contraception and sexual health clinics, specialist HIV services	6 years	Likely STD/HIV	No	NR	Scr. uptake: estimated at 14.0% Prevalence: 3.2% (285 8/90424; 95%CI: 3.04-3.27) **	Multivariable regr. analysis: - Male sex - Age 35+ - History of IDU	Those who tested positive were followed-up with clinicians (no data reported). Of the antiHCV positive individuals, 60.1% (1719/2858) were tested for HCV RNA. Outcomes: RNA rate: 69.2% (1191/1719) Start treatment: NR SVR: NR

Note: CI = confidence interval; NR = not reported; STD = sexually transmitted disease; BBV = blood-borne virus; IDU = injecting drug use; HCV = hepatitis C virus; HBV = hepatitis B virus; HAV = hepatitis A virus; HIV = human immunodeficiency virus; MSM = men who have sex with men; SVR = sustained virological response

* HCV-antibody prevalence is considered suboptimal (data were collected before 1994 when sensitivity/specificity of tests was not optimal, or reactive HCV-antibody test results were not confirmed by immunoblot).
** The reliability of the reported HCV-antibody prevalence is undecided (data were collected after 1993, but the diagnostic tests are unspecified, or other than described below, or dried blood spots or oral fluid samples were used).
*** HCV-antibody prevalence is considered valid; data were collected after 1993, and reactive HCV-antibody test results were confirmed by second or higher generation immunoblot assays from Ortho, Chiron, Novartis (RIBA), Innogenetics (LiaTek), Pasteur (DECISCAN HCV), Genelabs Diagnostics (HCV BLOT), or Mikrogen (recomBlot HCV IgG 2.0).

[a] History of IDU, body piercing/tattooing in unsanitary conditions, transfusion recipients before 1987, needlestick injury, hemodialysis patients, those born to mothers with documented HCV infection, individuals who reported ever having been told that they were infected with HCV yet lacked supporting documentation.

Table 2b. Integrated screening programs at general practitioner (GP) clinics

Program characteristics									Program outcomes		
First author, year of publication	**Calendar year of data collection**	**Population**	**Country and HCV prevalence according to CDC (1)**	**Setting of screening**	**Duration of screening program**	**Other tests**	**Pre-screening selection**	**Media activities**	**Screening uptake and anti-HCV prevalence (95% CI)**	**Risk profile of identified HCV cases / Risk factors associated with HCV**	**Follow-up of HCV-infected individuals**
Monnet, E, 2000 (90)	1997-1998	Patient of GP clinics, health centres, occupational physicians, prison health service, public laboratories	France (1.1%): Le Doubs	GP clinics, health centre, occupational physicians, prison health service, public laboratories	1 year	None	Yes, no previous positive HCV serology, and at least having one risk factor: transfusion before 1991, (ex-)IDU, (ex-)snorting cocaine, tattoo, HCV diagnosis in living environment	Yes	Scr. uptake: 82.5% (782/948) Prevalence: 4.0% (31/782; 95% CI: 2.8-5.6) *	Multivariable regr. analysis: - Age 30+ - Drug use	70.9% (22/31) attended the hepatologist for HCV RNA testing. Of those who tested HCV RNA positive, 10 had elevated ALAT of which 8 had a biopsy. Based on the results, 5 were indicated for treatment (no results reported). Outcomes: RNA rate: 86.4% (19/22) Start treatment: NR SVR: NR
Anderson, EM, 2009 (91)	2003-2004	GP patients aged 30-54 yrs	Scotland (1.1%): socio-economically deprived area of Glasgow	GP clinics (intervention clinic and comparison clinic)	6 months	None	No; in intervention practice all individuals aged 30-54 yrs who attended non-urgent appointments were offered HCV screening. In comparison practice, no intervention was carried out.	Eligible patients in intervention practice received information leaflet	Scr. uptake: Intervention clinic: 27.8% (117/421) Comparison clinic: not applicable Prevalence: Intervention clinic: 12.8% (15/117; 95% CI: 7.9-20.0) Comparison clinic: No individuals were tested during study period. **	Multivariable regr. analysis: - History of IDU	HCV RNA positive patients (n=11) were referred to a specialist and all attended ≥1 appointment. Four years later, 8 were lost to follow-up, 2 started treatment, and 1 achieved an SVR. Outcomes: RNA rate: 73.3% (11/15) Start treatment: 18.2% (2/11) SVR: 50.0% (1/2)
Pauti, M-D, 2008 (52)	2007	People with poor access to health care, mostly migrants	France (1.1%) : Saint-Denis and Paris areas	Health care and advice centers of Médecins du Monde [b]	4 years, but data from 1 year are reported	HIV, HBV	No	No	Scr. uptake: NR Prevalence: 5.9% (70/1196; 95% CI: 4.7-7.3) **	Listed risk factors: - North and Middle Africa - Sub-Saharan Africa - Eastern Europe	The objective of the project was to offer full access to treatment, but actual results are not reported. Outcomes: RNA rate: NR Start treatment: NR SVR: NR

Table 2b cont'd

Program characteristics									Program outcomes		
First author, year of publication	**Calendar year of data collection**	**Population**	**Country and HCV prevalence according to CDC (1)**	**Setting of screening**	**Duration of screening program**	**Other tests**	**Pre-screening selection**	**Media activities**	**Screening uptake and anti-HCV prevalence (95% CI)**	**Risk profile of identified HCV cases / Risk factors associated with HCV**	**Follow-up of HCV-infected individuals**
Uddin, G, 2010 (54) [a]	NR	GP patients	UK (1.1%): East London, West London, Walsall, Sandwell, Bradford	GP clinic (and at community centers, see Table 1a)	NR	HBV	Yes, immigrants from the Indian sub-continent (India, Bangladesh or Pakistan)	No	Scr. uptake: NR Prevalence: 0% (0/171; 95% CI: 0-2.19) **	Not applicable	Not applicable
Kallman, JB, 2010 (53) [a]	NR	GP patients	USA (1.9%): Northern Virginia	GP clinic (and general health screening at Asian health fairs, see Table 1a)	NR	HBV	Yes, Vietnamese	NR	Scr. uptake: NR Prevalence: 1.2% (3/245; 95% CI: 0.4-3.5) at GP clinic **	Univariable regr. analysis: - Elevated AST	Patients were seen by their primary care givers for further management, or referred for further follow-up and treatment (no results reported). Outcomes: RNA rate: NR Start treatment: NR SVR: NR
Ouzan, D, 2003 (92)	2000	GP patients aged over 18 years	France (1.1%): Alpes-Maritimes district	GP clinic	1 month	None	Yes: unknown HCV serology status, and at least one risk factor: blood transfusion before 1991, injecting or nasal DU, incarceration. Previously diagnosed HCV positives that visited the GP in the screening period were also followed-up.	No	Scr. uptake: 66.0% (233/353) Prevalence: 3.9% (9/233; 95% CI: 2.0-7.02) 9 were newly identified through screening; 229 were found with a previous diagnosis **	NR for newly identified	Patients were followed-up by their GP, referred to a specialist, or a hospital unit. Follow-up data are reported for newly and previously diagnosed patients together and available for 159/238. HCV RNA test results were known for n=106, and 82 were HCV RNA positive. A liver biopsy was performed in 62, of which 31 received treatment. Treatment was effective for 10, fairly effective for 12, and ineffective for 7. Outcomes: RNA rate: 77.4% (82/106) Start treatment: 37.8% (31/82) SVR: NR
Josset, V, 2004 (93)	1997	GP patients aged 18-70 yrs	France (1.1%): Haute-Normandie	GP clinic	10 days	None	Yes, no previous HCV serology performed, and at least one of the traditional risk factors present [c]	No	Scr. uptake: 72.7% (3550/4883) Prevalence: 1.4% (49/3550; 95% CI:1.0-1.8%) **	An evaluation of screening strategies based on risk factor data showed that screening those with a history of blood transfusion or drug use appeared to be the most efficient approach.	NR Outcomes: RNA rate: NR Start treatment: NR SVR: NR
Pradat, P, 2001 (94)	1997	GP patients aged 18-69 yrs	France (1.1%): Lyon area	GP clinics	6 months; each GP clinic offered HCV screening for 5 days	None	No	NR	Scr. uptake: 59.0% 6876/11646 Prevalence: 0.4% (30/6876; 95% CI: 0.3-0.6) ***	Listed risk factors: - History of IDU - Transfusion <1990 - Other risk factors	NR Outcomes: RNA rate: NR Start treatment: NR SVR: NR

Table 2b cont'd

Program characteristics									Program outcomes			
First author, year of publication	**Calendar year of data collection**	**Population**	**Country and HCV prevalence according to CDC (1)**	**Setting of screening**	**Duration of screening program**	**Other tests**	**Pre-screening selection**	**Media activities**	**Screening uptake and anti-HCV prevalence (95% CI)**	**Risk profile of identified HCV cases / Risk factors associated with HCV**	**Follow-up of HCV-infected individuals**	
Altman, C, 1999 (95)	1997	GP patients	France (1.1%): Val-de-Marne and Hauts-de-Seine	GP clinics	2 weeks	None	Yes, no previous HCV serology performed, and a history of IDU or transfusion before 1991	No	Scr. uptake: Transfusion group: 76.9% (226/294) History of IDU group: 50.0% (13/26) Prevalence: Transfusion group: 3.1% (7/226, 95% CI: 1.5-6.3) History of IDU group: 30.8% (4/13; 95% CI: 12.7-57.6) *	NR	NR Outcomes: RNA rate: Start treatment: SVR:	 NR NR NR
Helsper, CW, 2010 (96)	2007-2008	GP patients	Netherlands (1.1%): Amersfoort and Apeldoorn	GP clinics in intervention region with primary care practice support, and GP clinics in control region without practice support	4 months	None	Yes, individual risk estimation by GP	Yes	Scr. uptake: NR Prevalence: Intervention: 1.7% (3/172; 95% CI: 0.6-5.0) Control: 0.8% (1/118; 95% CI: 0.04-4.6) **	Data not available	NR Outcomes: RNA rate: Start treatment: SVR:	 NR NR NR
Sahajian, F, 2004 (9)	2000-2001	GP, private practitioners, and specialist patients	France (1.1%): Lyon area	GP clinics Intervention: A campaign including training aimed at GPs was designed to improve screening practices. The campaign also reached the public. Comparison: Data were compared to the 12-months period preceding the campaign.	12 months	None	Yes, history of IDU, blood products before 1991, or elevated serum transaminase levels	Yes	Scr. uptake: NR Prevalence: Intervention: 1.73% (276/15952; - 95% CI: 1.53 1.94) Comparison: 1.67% (231/13799; 95% CI:1.47-1.90) **	NR	NR Outcomes: RNA rate: Start treatment: SVR:	 NR NR NR

Table 2b cont'd

Program characteristics									Program outcomes		
First author, year of publication	**Calendar year of data collection**	**Population**	**Country and HCV prevalence according to CDC (1)**	**Setting of screening**	**Duration of screening program**	**Other tests**	**Pre-screening selection**	**Media activities**	**Screening uptake and anti-HCV prevalence (95% CI)**	**Risk profile of identified HCV cases / Risk factors associated with HCV**	**Follow-up of HCV-infected individuals**
Roudot-Thoraval, F, 2000 (98)	1997-1998	GP patients aged 6-85 years	France (1.1%): Le Doubs and n° 6 d'Ile-de-France	GP clinics Intervention 1: GPs asked their patients for risk factors for HCV and offered screening to those at risk. Intervention 2: Posters and leaflets in GPs waiting rooms, motivating those with a risk to discuss testing with their GP.	15 months	None	Yes, several risk factors (not all are listed), among which a history of IDU, transfusion, tattoo, HCV in social environment	Yes (intervention 2)	Scr. uptake: NR Prevalence: Intervention 1: 5.7% (15/261; 95% CI: 3.51-9.26) Intervention 2: 4.4% (10/228; 95% CI: 2.40-7.88) **	Listed risk factors: - History of IDU - Transfusion before 1991 - elevated ALT or symptoms - Tattoo - Other	NR Outcomes: RNA rate: NR Start treatment: NR SVR:

Note: CI = confidence interval; NR = not reported; IDU = injecting drug use; HCV = hepatitis C virus; HBV = hepatitis B virus; HIV = human immunodeficiency virus; ALT = alanine aminotransferase; AST = aspartate aminotransferase; SVR = sustained virological response

* HCV-antibody prevalence is considered suboptimal (data were collected before 1994 when sensitivity/specificity of tests was not optimal, or reactive HCV-antibody test results were not confirmed by immunoblot).

** The reliability of the reported HCV-antibody prevalence is undecided (data were collected after 1993, but the diagnostic tests are unspecified, or other than described below, or dried blood spots or oral fluid samples were used).

*** HCV-antibody prevalence is considered valid; data were collected after 1993, and reactive HCV-antibody test results were confirmed by second or higher generation immunoblot assays from Ortho, Chiron, Novartis (RIBA), Innogenetics (LiaTek), Pasteur (DECISCAN HCV), Genelabs Diagnostics (HCV BLOT), or Mikrogen (recomBlot HCV IgG 2.0).

[a]

[b] These programs combined a nonintegrated screening approach with integrated screening at the GP clinic (see Table 2b). Here only results of the nonintegrated screening are presented.

[c] Médecins du Monde ('Doctors of the World') is an international humanitarian organization providing medical care to vulnerable populations.

Transfusion before 1991, history of drug use, history of gastroscopy, contact with HCV infected person (spouse or other family member, occupational exposure, active or former imprisonment, history of invasive procedures (catheterism, fluid aspiration/cytology, biopsy), history of colonoscopy, history of surgery.

Table 2c. Integrated screening programs at VA health centers

Program characteristics								Program outcomes		
First author, year of publication	Calendar year of data collection	Population	Country and HCV prevalence according to CDC (1)	Setting of screening	Duration of screening program	Other tests	Prescreening selection	Media activities	Screening uptake and anti-HCV prevalence (95% CI)	Risk profile of identified HCV cases / Risk factors associated with HCV	Follow-up of HCV-infected individuals
Groom, H, 2008 (99)	2000-2001	Veterans	USA (1.9%): Minneapolis	Veteran Affairs Medical Center	2 years	None	Yes, only those with a risk factor were screened (risk factors not specified)	NR	Scr. uptake: NR Prevalence: 5.5% (681/12485; 95% CI: 5.1-5.9) *	NR	In total, 520/681 were HCV RNA positive of which 430 referred to a specialist, of which 88.8% (382/430) attended an appointment. Of those, 32.5% (124/382) received treatment which was successful in 37.0% (46/124) (SVR). Outcomes: RNA rate: 76.4% (520/681) Start treatment: 32.5% (124/382) SVR: 37.1% (46/124)
Mallette, C, 2008 (100)	1998-2004	Veterans	USA (1.9%): Providence	GP patients presenting to VA facilities	5 years and 8 months	None	Yes, only those with a risk factor were screened [a]	NR	Scr. uptake: 66.7% (5646/8471) Prevalence: 7.3% (412/5646; 95% CI:6.6-8.0); without already known positives: 260/5646 = 4.6% (95%CI=4.1-5.2%) ***	Listed risk factors: - History of IDU - Blood transfusion before 1992 - Intranasal cocaine use - Multiple sex partners - Tattoos	Of the newly diagnosed, 46.9% (122/260) had chronic HCV, of which 46.7% (57/122) were treatment eligible. Of those, 31.6% (18/57) received treatment and 33.3% (6/18) reached an SVR. Outcomes: RNA rate: 46.9% (122/260) Start treatment: 14.8% (18/122) SVR: 33.3% (6/18)
Cheung, RC, 2006 (101)	2000-2001	Veterans	USA (1.9%): Palo Alto	VA medical centre	12 months	None	Yes, if not previously tested, and if one or more risk factors were reported [b]	NR	Scr. uptake: NR Prevalence: 5.0% (536/10751; 95% CI: 4.6-5.4) ***	NR	In total, 362/536 patients were evaluated of which 84.8% (307/362) had chronic HCV. Of those, 18.6% (57/307) were treatment eligible of whom 24.6% (14/57) completed treatment with long-term follow-up, and 35.7% (5/14) achieved SVR. Outcomes: RNA rate: 84.8% (307/362) Start treatment: NR SVR: 35.7% (5/14)

Table 2c cont'd

Program characteristics									Program outcomes			
First author, year of publication	Calendar year of data collection	Population	Country and HCV prevalence according to CDC (1)	Setting of screening	Duration of screening program	Other tests	Prescreening selection	Media activities	Screening uptake and anti-HCV prevalence (95% CI)	Risk profile of identified HCV cases / Risk factors associated with HCV	Follow-up of HCV-infected individuals	
Rifai, M, 2006 (102)	2000-2001	Veterans	USA (1.9%): Virginia	Rural VA Medical Centre	22 months	None	Yes, only non-IDU substance using veterans who were admitted to a substance-use residential and rehabilitation treatment program were tested	NR	Scr. uptake: 99.4% (338/340) Prevalence: 23.1% CHCV (78/338; 95% CI: 18.9-27.9) (incl. 2 who knew already) ****	Univariate regr. analysis: - Cocaine snorting - History of IDU	In total, 48.7% (38/78) of the patients remained abstinent for 6 months and 30 were indicated for treatment and received treatment. In 46.7% (14/30) treatment was successful (SVR). Outcomes: RNA rate: n/a Start treatment: 81.1% (30/37) SVR: 46.7% (14/30)	
Zuniga, IA, 2006 (103)	2001-2003	Veterans	USA (1.9%): Suffolk County, Long Island	Primary-care outpatient departments of the Northport VA Medical Center (suburban VA hospital)	27 months	None	Yes, only those with a risk factor were screened [c]	No	Scr. uptake: 41.9% (2263/5400) Prevalence: 4.6% CHCV (103/2263; 95% CI: 3.8-5.5) ****	Multivariable regr. analysis - Age 40-54 yrs - Black race - History of IDU - Service during Vietnam era - Blood transfusion prior to 1992 - Tattoo or repeated body piercing - History of abnormal LFTs	NR Outcomes: RNA rate: n/a Start treatment: NR SVR: NR	

Note:CI = confidence interval; NR = not reported; VA = veterans affairs; IDU = injecting drug use; HCV = hepatitis C virus; CHCV = chronic hepatitis C virus; HIV = human immunodeficiency virus; LFT = liver function test; SVR = sustained virological response; PCR = polymerase chain reaction

* HCV-antibody prevalence is considered suboptimal (data were collected before 1994 when sensitivity/specificity of tests was not optimal, or reactive HCV-antibody test results were not confirmed by immunoblot).
*** HCV-antibody prevalence is considered valid; data were collected after 1993, and reactive HCV-antibody test results were confirmed by second or higher generation immunoblot assays from Ortho, Chiron, Novartis (RIBA), Innogenetics (LiaTek), Pasteur (DECISCAN HCV), Genelabs Diagnostics (HCV BLOT), or Mikrogen (recomBlot HCV IgG 2.0).
**** HCV-antibody prevalence is considered valid, but reflecting chronic HCV infection (data were collected after 1993, and reactive HCV antibody test results were confirmed by PCR).

[a] Vietnam-era veteran, transfusion of blood of blood products before 1992, history of IDU, history of snorting cocaine, history of 5 or more drinks a day for 10 or more years in your lifetime, history of multiple (10 or more) sexual partners in your lifetime, a man who has sex with men, history of exposure to blood on skin or mucous membranes, required chronic hemodialysis, have a tattoo or body piercing, have had a positive test for HIV or hepatitis B, have been told that you have unexplained liver disease.
[b] Blood transfusion prior to 1992, IV drug use (even once), snorting of cocaine, blood exposure, sexual promiscuity (>10 lifetime sex partners), renal dialysis, tattoo or body piercing, excessive alcohol use.
[c] Vietnam-era veteran, transfusion of blood products prior to 1992, history of IDU, blood exposure in or through skin or mucous membranes, multiple sexual partners (past or present), hemodialysis, tattoo or repeated body piercing, intranasal cocaine use (past or present), unexplained liver disease, having been told that he/she has abnormal liver function tests, intemperate alcohol use (more than seven alcoholic beverages per week).

Table 2d. Integrated screening programs in antenatal/obstetric/fertility clinics

Program characteristics									Program outcomes		
First author, year of publication	**Calendar year of data collection**	**Population**	**Country and HCV prevalence according to CDC (1)**	**Setting of screening**	**Duration of screening program**	**Other tests**	**Prescreening selection**	**Media activities**	**Screening uptake and anti-HCV prevalence (95% CI)**	**Risk profile of identified HCV cases / Risk factors associated with HCV**	**Follow-up of HCV-infected individuals**
Alexanian, AA, 2009 (abstract) (104)	NR	Pregnant women	UK (1.1%): London	Antenatal clinic	8 years, Hospital records search	HBV, HIV	No	NR	Scr. uptake: NR Prevalence: 0.4 (115/31081; 95% CI: 0.3-0.4) *	NR	In total, 73.0% (84/115) of patients had chronic HCV, of whom 55.9% (47/84) were lost to follow-up, 10.7% (9/84) deferred treatment, 4.8% (4/84) were on treatment, and 17.9% (15/84) completed treatment. Of these 15, 12 achieved SRV, 1 relapsed, and two failed to respond. Outcomes: RNA rate: 73.0% (84/115) Start treatment: 67.9% (19/28) SVR: 80.0% (12/15)
Abusheikha, N, 1999 (105)	1996-1998	Couples receiving fertility treatment	UK (1.1%): Cambridge	Bourn Hall clinic, infertility hospital	3 years	HIV, HBV	No	NR	Scr. uptake: NR Prevalence: 0.5% (9/1658; 95% CI: 0.3-1.0) **	NR	All patients were counseled by senior medical staff. Outcomes: RNA rate: NR Start treatment: NR SVR: NR
Leikin, EL, 1994 (106)	1991-1992	Pregnant women who are at risk for perinatal complications	USA (1.9%): Valhalla	Hospital (obstetric)	19,5 months	ALT	No	NR	Scr. uptake: NR Prevalence: 4.6% (78/1700; 95% CI: 3.7-5.7) *	Multivariable regr. analysis: - History of IDU - Other drug use - Age>30 - Incarceration - Blood transfusion	In total, 96.2% (75/78) of the patients returned for follow-up. No further details reported. Outcomes: RNA rate: NR Start treatment: NR SVR: NR
Ward, C, 2000 (107)	1997-1999	Pregnant women	UK (1.1%): London	Antenatal clinic	18 months	HBV	No	Yes	Scr. uptake: 98.0% (4727/4825) Prevalence: 0.8% (38/4729; 95% CI:0.6-1.1) ***	Univariate regr. analysis: - History of IDU - HCV-infected partner - Tattoo - Partner IDU	In total, 71.1% (27/38) had chronic HCV, and 85.2% (23/27) were offered follow-up appointments so far. Of those, 82.6% (19/23) attended for further investigations. Outcomes: RNA rate: 71.1% (27/38) Start treatment: NR SVR: NR

Table 2d cont'd

Program characteristics									Program outcomes		
First author, year of publication	**Calendar year of data collection**	**Population**	**Country and HCV prevalence according to CDC (1)**	**Setting of screening**	**Duration of screening program**	**Other tests**	**Prescreening selection**	**Media activities**	**Screening uptake and anti-HCV prevalence (95% CI)**	**Risk profile of identified HCV cases / Risk factors associated with HCV**	**Follow-up of HCV-infected individuals**
Costa, ZB, 2009 (108)	2004-2005	Pregnant women	Brazil (1%): Central Brazil, Goiania	Antenatal clinics	NR	HIV and seven other infectious diseases (not specified)	No	NR	Scr. uptake: 99.9% (28561/28576) Prevalence: 0.2% CHCV (43/28561; 95% CI:0.1-0.2%) ****	Multivariable regr. analysis: - Older age - >3 pregnancies (no data on risk factors collected)	Patients were referred for free of cost medical counseling (no results reported). Outcomes: RNA rate: n/a Start treatment: NR SVR: NR

Note: CI = confidence interval; NR = not reported; IDU = injecting drug use; HCV = hepatitis C virus; CHCV = chronic hepatitis C virus; HIV = human immunodeficiency virus; HBV = hepatitis B virus; ALT = alanine aminotransferase; SVR = sustained virological response; PCR = polymerase chain reaction

* HCV-antibody prevalence is considered suboptimal (data were collected before 1994 when sensitivity/specificity of tests was not optimal, or reactive HCV-antibody test results were not confirmed by immunoblot).
** The reliability of the reported HCV-antibody prevalence is undecided (data were collected after 1993, but the diagnostic tests are unspecified, or other than described below, or dried blood spots or oral fluid samples were used).
*** HCV-antibody prevalence is considered valid; data were collected after 1993, and reactive HCV-antibody test results were confirmed by second or higher generation immunoblot assays from Ortho, Chiron, Novartis (RIBA), Innogenetics (LiaTek), Pasteur (DECISCAN HCV), Genelabs Diagnostics (HCV BLOT), or Mikrogen (recomBlot HCV IgG 2.0).
**** HCV-antibody prevalence is considered valid, but reflecting chronic HCV infection (data were collected after 1993, and reactive HCV antibody test results were confirmed by PCR).

Table 2e. Integrated screening programs in psychiatric clinics

Program characteristics									Program outcomes		
First author, year of publication	**Calendar year of data collection**	**Population**	**Country and HCV prevalence according to CDC (1)**	**Setting of screening**	**Duration of screening program**	**Other tests**	**Prescreening selection**	**Media activities**	**Screening uptake and anti-HCV prevalence (95% CI)**	**Risk profile of identified HCV cases / Risk factors associated with HCV**	**Follow-up of HCV-infected individuals**
Freudenreich, O, 2007 (109)	2003-2004	Psychiatric patients (most schizophrenia)	USA (1.9%): Boston	Clozapine outpatient clinic (psychiatric patients)	4 months	None	No	NR	Scr. uptake: 100% (98/98) Prevalence: 8.2% (8/98; 95% CI: 4.2-15.3) (incl the one known before) *	Most common risk factors: - Polysubstance abuse	All patients were referred to a specialist; after two years, none had started treatment. One patient became unstable psychologically after the discovery of his infection. Outcomes: RNA rate: 50.0% (4/8) Start treatment: 0% (0/8) SVR: -
Gunewardene, R, 2010 (110)	NR	Psychiatric patients	Australia (2%): in a capital city	Acute psychiatric inpatient unit within an Area Health service in Australia. Comparison of two strategies.	6 months	None	Unit A: No; Unit B: Yes (IDU, exposure to contaminated blood products)	NR	Scr. uptake: Unit A: 79.8% (95/119) Unit B: 90.0% (36/40) Prevalence: Unit A: 3.2% (3/95; 95% CI: 1.1-8.9); Unit B: 41.7% (15/36; 95% CI:27.1-57.8) **	Most common risk factors: - History of IDU	All patients were offered post-test counseling and were referred to a specialist (no results reported). Outcomes: RNA rate: NR Start treatment: NR SVR: NR
Lacey, C, 2007 (111)	2002-2003	Psychiatric patients	Australia (2%): Melbourne, Victoria	Inner city public hospital (psychiatric)	6 months	None	Yes; Patients admitted with psychotic or affective disorders, >18 yrs, inpatient stay >2 days, and did not have known HCV infection	Yes	Scr. uptake: 20.5% (71/346) Prevalence: 19.7% (14/71; 95% CI: 12.1-30.4) *	Most common risk factors: - History of IDU - Sharing injection equipment	All positive patients received post-test counseling and were referred to a specialist (no results reported). Outcomes: RNA rate: NR Start treatment: NR SVR: NR

Note: CI = confidence interval; NR = not reported; IDU = injecting drug use; HCV = hepatitis C virus; SVR = sustained virological response

* HCV-antibody prevalence is considered suboptimal (data were collected before 1994 when sensitivity/specificity of tests was not optimal, or reactive HCV-antibody test results were not confirmed by immunoblot).
** The reliability of the reported HCV-antibody prevalence is undecided (data were collected after 1993, but the diagnostic tests are unspecified, or other than described below (see ***), or dried blood spots or oral fluid samples were used).
*** HCV-antibody prevalence is considered valid; data were collected after 1993, and reactive HCV-antibody test results were confirmed by second or higher generation immunoblot assays from Ortho, Chiron, Novartis (RIBA), Innogenetics (LiaTek), Pasteur (DECISCAN HCV), Genelabs Diagnostics (HCV BLOT), or Mikrogen (recomBlot HCV IgG 2.0).

Table 2f. Integrated screening programs integrated in other clinics or services

Program characteristics									Program outcomes		
First author, year of publication	Calendar year of data collection	Population	Country and HCV prevalence according to CDC (1)	Setting of screening	Duration of screening program	Other tests	Pre-screening selection	Media activities	Screening uptake and anti-HCV prevalence (95% CI)	Risk profile of identified HCV cases / Risk factors associated with HCV	Follow-up of HCV-infected individuals
Capron, D, 1999 (112)	1996	Patients > 14 y admitted to an emergency unit	France (1.1%): Picardy	Emergency health unit hospital	At least one week per unit (7 units) over a period of 2 months	None	Yes, only those with a reported risk factor were tested	NR	Scr. uptake: NR Prevalence: 2.4% (11/451; 95% CI: 1.4-4.3) *	Most common risk factors: - Blood transfusion - History of drug addiction - Surgery - Endoscopy	All patients were referred for medical follow-up. In total, 36.4% (4/11) attended, of which 50.0% (2/4) had chronic HCV. Liver biopsy showed minimal activity, and treatment was not indicated. Outcomes: RNA rate: 50.0% (2/4) Start treatment: 0% (0/2) SVR: -
Alswaidi, FM, 2010 (113)	2008	Individuals from the general population that wish to get married	Saudi Arabia (0.9%): throughout the country	Mandatory premarital national screening program	4 months	HBV, HIV	No	NR	Scr. uptake: NR Prevalence: 0.3% (250/74662; 95% CI: 0.3-0.4) **	NR	Counseling sessions were offered to provide education to prevent infection transmission, and HCV infected couples are encouraged to avoid marriage. No results on medical follow-up reported. Outcomes: RNA rate: NR Start treatment: NR SVR: NR
Dubois, F, 1994 (114)	NR	Healthy subject of routine medical check up	France (1.1%): Western part	Routine medical check up	5 weeks	ALT, HAV, HBV, HDV	Yes: elevated ALT levels (vs control group without elevated ALT)	NR	Scr. uptake: NR Prevalence: 4.9% (15/308; 95% CI: 3.0-7.9) *** Control group: 0.3% (1/308)	Most common risk factors: - Blood transfusion - History of IDU	Patients were referred to their family physician (no results reported). Outcomes: RNA rate: 73.3% (11/15) RNA rate control gr: 0% (0/1) Start treatment: NR SVR: NR
Roberts, J, 2010 (115) (abstract)	2009	MSM attending service and who were tested for HIV	UK (1.1%): Brighton	Local outreach services for HIV point of care testing	4 months	HAV, HBV, syphilis, HIV	No	NR	Scr. uptake: 66.2% (55/82) Prevalence: 1.8% CHCV (1/55; 95% CI: 0.1-9.6) ****	NR	Subsequent attendance at STI services remained low. Follow-up of the HCV-infected person was not reported in detail. Outcomes: RNA rate: - Start treatment: NR SVR: NR

Table 2f cont'd

Program characteristics									Program outcomes		
First author, year of publication	**Calendar year of data collection**	**Population**	**Country and HCV prevalence according to CDC (1)**	**Setting of screening**	**Duration of screening program**	**Other tests**	**Pre-screening selection**	**Media activities**	**Screening uptake and anti-HCV prevalence (95% CI)**	**Risk profile of identified HCV cases / Risk factors associated with HCV**	**Follow-up of HCV-infected individuals**
Cohen, DE, 2006 (116)	2001	MSM	USA (1.9%): Greater Boston area	Community care facility	8 months	None	No	Yes	Scr. uptake: NR Prevalence: 11.5% (25/218; 95% CI: 7.9-16.4) ***	Univariate regr. analysis: - HIV infection - HBV infection - Less receptive anal sex - Lifetime history of gonorrhoea - History of IDU - Reporting blood on shared cocaine straws - Crack cocaine use in prior 6 months	Patients were referred to their primary care provider (no results reported). Outcomes: RNA rate: NR Start treatment: NR SVR: NR
Campello, C, 2002 (117)	1994-1995	Individuals ages 17-67 years, currently employed in the processing and/or trade of food and beverages	Italy (1.1%): Lombardia region, administrative boundary of the former USL 22 (local health unit)	Periodic compulsory health check for the surveillance and control of diseases transmitted by the fecal-oral route as well as tuberculosis	14 months	None	No	NR	Scr. uptake: 77.6% (2154/2776) Prevalence: 3.3% (71/2154; 95% CI 2.6-4.1) ***	Multivariable regr. analysis: - Age >50 years - Blood transfusion - History of IDU - Tattooing - <8 years of education - Female sex	Patients offered the possibility of undergoing a follow-up for the clinical and laboratory evaluation of hepatic involvement (no results reported). Outcomes: RNA rate: 71.8% (51/71) Start treatment: NR SVR: NR
Tafuri, S, 2010 (118)	2008	Asylum seekers without signs or symptoms in recent or remote past	Italy (1.1%): Bari	Asylum seeker center	3 months	HBV, HIV, syphilis	No	NR	Scr. uptake: 71.1% (529/744) Prevalence: 4.5% (24/529; 95% CI: 3.06-6.07) *	NR	All patients who tested positive were treated (no results were reported). Outcomes: RNA rate: NR Start treatment: NR SVR: NR

Note: CI = confidence interval; NR = not reported; IDU = injecting drug use; HCV = hepatitis C virus; CHCV = chronic hepatitis C virus; HBV = hepatitis B virus; HAV = hepatitis A virus; HDV = hepatitis delta virus; HIV = human immunodeficiency virus; ALT = alanine aminotransferase; MSM = men who have sex with men; SVR = sustained virological response; PCR = polymerase chain reaction

* HCV-antibody prevalence is considered suboptimal (data were collected before 1994 when sensitivity/specificity of tests was not optimal, or reactive HCV-antibody test results were not confirmed by immunoblot).
** The reliability of the reported HCV-antibody prevalence is undecided (data were collected after 1993, but the diagnostic tests are unspecified, or other than described below, or dried blood spots or oral fluid samples were used).
*** HCV-antibody prevalence is considered valid; data were collected after 1993, and reactive HCV-antibody test results were confirmed by second or higher generation immunoblot assays from Ortho, Chiron, Novartis (RIBA), Innogenetics (LiaTek), Pasteur (DECISCAN HCV), Genelabs Diagnostics (HCV BLOT), or Mikrogen (recomBlot HCV IgG 2.0).
**** HCV-antibody prevalence is considered valid, but reflecting chronic HCV infection (data were collected after 1993, and reactive HCV antibody test results were confirmed by PCR).

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CHAPTER 3

RISK-BASED AND INTERNET-BASED SCREENING FOR HEPATITIS C

CHAPTER 3.1

Evaluation of a risk assessment questionnaire to assist hepatitis C screening in the general population

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Evaluation of a risk assessment questionnaire to assist hepatitis C screening in the general population

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Many individuals with hepatitis C virus (HCV) infection are undiagnosed. This study evaluates a risk assessment questionnaire, developed for use online to target blood-screening for HCV. Two hundred and eighty-nine patients with known HCV status completed a written questionnaire on prominent HCV risk factors. Questionnaires generated advice to seek testing if at least one risk factor was reported. Agreement of the testing advice with the HCV status of respondents was evaluated. Subsequently, we validated our questionnaire among 985 patients of an outpatient clinic for sexually transmitted infections. The post-test-probability-of-disease (PTPD) and diagnostic gain (PTPD minus prior probability of disease) were calculated. The questionnaire's sensitivity and specificity were 84.6% and 63.8%, respectively, and higher in the STI clinic patients. The PTPD of positive testing advice was 72.5% given HCV prevalence of 53.0%, yielding a diagnostic gain of 19.5%. Applying the estimated prevalence in the general Dutch population (0.1-0.4%), and the anticipated prevalence in the online project (1.0-6.0%), yielded diagnostic gains of 0.13-0.53% and 1.3-7.0%, respectively. We conclude that our questionnaire succeeded in selecting at-risk individuals as its testing advice agreed well with the HCV status. We suggest that the questionnaire be used online as a selection tool for HCV blood-screening in the general population.

Introduction

Hepatitis C virus (HCV) infection, first identified in 1989, is caused by a bloodborne virus and affects an estimated 120 million individuals worldwide [1]. Almost 75% of HCV infections become chronic [2].

Twenty to 30 years after infection, chronic HCV leads to liver cirrhosis in 20%-30% of patients, 2%-5% of whom each year will progress to liver failure or liver carcinoma [3]. Since the onset of the infection itself and the development of cirrhosis in chronically infected patients are usually asymptomatic [3,4], many cases are undetected. Earlier diagnosis of HCV enables patients to start timely treatment, adopt a healthy lifestyle (e.g., avoiding alcohol [5]), and prevent possible transmission to others. Treatment options for HCV have improved substantially since 2001 [5,6], and the Dutch Health Council has recommended that more education and tracing be focused on groups at risk for HCV infection [7]. In most western European countries, the prevalence of HCV infection is low, estimated at 0.1%-0.4% in the Netherlands [8], 0.8% in France [9], and 0.6%-1.1% in the UK [10]. For low-prevalence countries, it is worth considering whether selective screening (i.e., establishing individual risk for HCV infection as a condition for screening) may be more cost-effective than mass screening (i.e. every inhabitant is advised to test for HCV) [11,12]. Therefore, as a pilot project in the Netherlands, an HCV internet programme was set up to identify HCV-infected individuals in the general population by testing individuals at risk for HCV. The programme's strategy consists of a public media campaign to refer individuals from the general population who are potentially at risk of HCV, to an online interactive risk assessment questionnaire at www.heptest.nl. The questionnaire determines whether or not individuals are at risk for HCV and offers an opportunity for anonymous blood testing, free of charge.

This study describes the development and evaluation of the HCV risk assessment questionnaire before its use online. We determined the questionnaire's discriminative value for diagnosing HCV. Furthermore, we evaluated its relevance in clinical practice. This paper

discusses implications for use of the questionnaire online.

Methods

Development of the HCV risk assessment questionnaire

The questionnaire was developed in three stages. Firstly, the content was developed. Secondly, the questions were formulated and tested on members of the public for comprehensibility. This resulted in a core questionnaire, which was sent out to patients for the evaluation study. Meanwhile, however, new data on risk factors had become available. Thirdly, therefore, an extended questionnaire was developed. The following paragraphs describe these three stages in the developmental process.

Content

Development of the core questionnaire was based on a literature review of risk factors for HCV, followed by a meeting of experts, in which the risk factors from the literature were discussed for inclusion in the questionnaire. The expert group consisted of eight health care professionals (professor in hepatology, professor in epidemiology and prevention of infectious diseases, senior epidemiologist, two medical doctors who specialised in infectious diseases and public health, coordinator of the National Hepatitis Centre, senior social psychologist specialising in online research, health communication expert). The expert group decided to include risk factors/groups either if the expected prevalence in the specific group was considered to be high (e.g. injecting drug users (IDUs)) or if not informing a specific group was considered to be unethical (e.g. individuals who were administered blood products before 1992 as these individuals have never been informed in the Netherlands and have the right to know about their risk). Some risk factors described in literature (e.g. dental care [13]) were not included, or included only when they occurred in countries with a medium to high

Table 1

Risk factors/behaviours included in the core and extended risk assessment questionnaires; associated HCV prevalences (where known), HCV risk questionnaire evaluation study, the Netherlands, 2006-2007

Risk factor	HCV prevalence
IDU	Occasional users: 1.5%-14.1% [14] Frequent users: 31%-98% [15]
Being born in a HCV-endemic country	HCV endemic countries: Egypt (18%), Bolivia (11%), Rwanda (17%), Burundi (11%), Cameroon (13%), Guinea (11%), Mongolia (11%) [16]
Having received blood (products) before 1992	0.02%-0.2% [8]
HCV-infected mother	Mother HIV-neg: ~4% Mother HIV-pos: ~20% [17]
Mother is/was IDU	Prevalence may be slightly lower than the above (4%-20%) as the HCV prevalence among IDU is high but not 100%
Living together for >1 year and sharing bathroom items with HCV-infected individuals	0%-11% [15]
Living together for >1 year and sharing bathroom items with IDU	Prevalence may be slightly lower than the above (0%-11%), as the HCV prevalence among IDU is high but not 100%
Needlestick injury: needle exposed to high-risk person (IDU, haemophiliac, dialysis patient, HCV-infected individual)	Prevalence unknown. Transmission rate with HCV-contaminated needle: 1%-10% [18,19]
Needlestick injury in HCV-endemic country	Prevalence data of HCV-endemic countries: see above. Transmission rate with HCV-contaminated needle: 1%-10% [18,19]
Haemophilia patient	~70% [20,21]
Haemodialysis patient	2.6%-22.9% [22]
Organ recipient	Prevalence unknown
Having received blood (products) in medium/high risk country [a]	Prevalence unknown
Exposure of healthcare workers to blood/tissue in medium/high risk country [a]	Prevalence unknown
Surgical/dental procedure in medium/high risk country [a]	Prevalence unknown
Ritual intervention such as circumcision or scarification in medium/high risk country [a]	Prevalence unknown
Tattoo in medium/high risk country [a]	Prevalence unknown
Body-piercing in medium/high risk country [a]	Prevalence unknown
HCV risk factors added in the extended HCV risk assessment questionnaire:	
HIV-positive status	33% [23]
NIDU ≥ 3 times a week for ≥3 months	2.3%-35.3% [24]

CDC: United States Centers for Disease Control and Prevention; HCV: Hepatitis C virus; HDI: Human development index; HIV: Human immunodeficiency virus; IDU: Injecting drug user; NIDU: Non-injecting illicit drug use; WHO World Health Organization.

[a] Indicated as risk for HCV infection if happened in countries with low or medium HDI or with an estimated HCV prevalence >2% according to either country-specific estimates of the WHO [16] or regional estimates of the CDC [1].

prevalence of HCV infection, as including these risks would be tantamount to advising almost everyone to be tested for HCV, yielding low discriminative power to the questionnaire. The experts reached consensus for all risk factors. The upper panel of table 1 shows the risk factors selected for inclusion in the core questionnaire, and the prevalence of HCV infection associated with each risk factor. For study purposes, we also included questions on demographics (age, sex, educational level) and whether or not individuals were infected with hepatitis B virus (HBV).

Pre-testing

To improve its comprehensibility, the core questionnaire was pre-tested on 20 people (11 male) recruited at a popular Amsterdam street market that attracts a demographically diverse population and at the liver outpatient clinic of the Academic Medical Center of Amsterdam. All questions were read by the participants, and comprehension was examined by asking them to comment if they did not fully understand any detail. If concepts thought likely to be difficult were not queried by a participant, the interviewer asked him/her to describe their meaning. Terminology found difficult to comprehend was altered according to suggestions by participants. After pre-testing, the core questionnaire was ready for evaluation.

Development of the extended HCV risk assessment questionnaire

After the initial development of the core questionnaire, data were published that indicated a relatively high prevalence of HCV infection in non-injecting illicit drug users (NIDU) and HIV-infected patients [25,26]. We therefore extended the core questionnaire with these two risk factors. Furthermore, in this extended questionnaire, we asked patients how they thought they had become infected, seeking risks for HCV infection that were not covered by the core questionnaire. The lower panel of table 1 shows the risk factors that were added in the extended questionnaire.

Evaluation study

To evaluate both the core and the extended questionnaire, individuals whose HCV infection status was known (i.e. liver disease patients) were approached and asked to fill out the questionnaire. Firstly, the sensitivity and specificity of both the core and the extended questionnaire were determined. Secondly, clinical relevance was evaluated by determining the diagnostic gain (i.e. the improvement in knowledge/certainty as to whether or not an individual was infected with HCV, resulting from the use of the questionnaire). Thirdly, a validation study was performed using data from patients attending a clinic for sexually transmitted infections (STI).

Recruitment of the liver disease patients

Between October 2006 and October 2007, Dutch speaking patients suffering from liver-related diseases (such as HCV or HBV infection) were recruited at various locations. These people were selected because they were presumed to have been tested for HCV and to know their HCV status.

From October 2006 to June 2007 the core questionnaire was distributed at two liver outpatient clinics in Amsterdam, and was handed out during the National Hepatitis Week's patient symposium 2007. From July to October 2007 the extended questionnaire was sent to 459 members of the Dutch liver patient organisation (Nederlandse Leverpatiëntenvereniging), with an explanation about the evaluation study and a request to cooperate by filling out and returning the questionnaires by post.

Validation study in STI clinic patients

In order to validate the questionnaire in a population more representative of the general Dutch population with respect to liver disease prevalence, data from an anonymous survey conducted from April to May 2007 among 985 patients at the outpatient clinic for STI of the Public Health Service of Amsterdam were used retrospectively. This survey collected detailed data about sexual risk behaviour and risk factors for HCV and blood tests for HIV, HCV, and other STI. HCV antibody screening was performed by means of a third-generation commercial microparticle EIA system (AxSym HCV version 3.0), and positive test results were confirmed by Immunoblot (Chiron RIBA HCV 3.0 SIA). The prevalence of HCV infection among the STI clinic patients was 1.0%. The data collected on HCV risk factors were used to assess whether an individual would have been advised to test for HCV according to the extended risk assessment questionnaire.

Statistical methods

All participants who reported at least one risk factor were advised to be tested for HCV infection ('positive testing advice'; PTA), and those who reported no risk factors were advised that testing was unnecessary ('negative testing advice'; NTA). Where answers to questions were missing or inconclusive (i.e., the answer 'don't know'), we assumed that the risk was not present. Differences in risk factor prevalence between the HCV-positive and the HCV-negative group were tested using Pearson chi-square test or, when numbers were small, Fisher's Exact two-tailed test. For testing differences in age, the Mann-Whitney-U test was used. We calculated Likelihood Ratio-based 95% confidence intervals (CI) for sensitivity and specificity. To examine whether sensitivity and specificity differed with sex and age, we performed stratified sensitivity and specificity analyses for sex and age (≤50 and >50 years, cut-off based on median age). Furthermore, we performed two multivariate logistic regression analyses, separately for HCV positives and for HCV negatives/unknown, with sex and age (continuous variable) as predictors of testing advice (outcome variable).

The sensitivity of the core and extended questionnaires – i.e., the percentage of HCV-positive patients

being correctly identified as HCV-positive – was calculated as True PTA/(True PTA+False NTA). The specificity – i.e. the percentage of HCV-negative patients being correctly identified as HCV negative – was calculated as True NTA/(True NTA+False PTA).

For the validation study, we calculated sensitivity and specificity of the extended questionnaire in the STI clinic patients. Some minor risk details had not been questioned in the STI clinic survey (e.g. living together for >1 year and sharing bathroom items with HCV-infected individuals or IDU). Data from the liver disease patients were restricted to the same risk factors to calculate a comparable sensitivity and specificity. Differences between sensitivity and specificity from liver disease patients and STI clinic patients were evaluated using Newcombe's method 10 for independent proportions [27].

Sensitivity and specificity represent the diagnostic accuracy of a screening questionnaire, but they do not reflect the individual likelihood of disease associated with a certain questionnaire result and are therefore less useful in clinical practice. The clinical relevance of the questionnaire was assessed by calculating the post-test probability of disease (PTPD; i.e. the likelihood of being HCV-positive when given a positive or negative HCV testing advice [28]) using the formulas:

$$\text{PTPD after positive testing advice: } \frac{\text{sensitivity} \times \text{prevalence}}{\text{sensitivity} \times \text{prevalence} + (1 - \text{specificity}) \times (1 - \text{prevalence})}$$

$$\text{PTPD after negative testing advice: } 1 - \frac{\text{specificity} \times (1 - \text{prevalence})}{(1 - \text{sensitivity}) \times \text{prevalence} + \text{specificity} \times (1 - \text{prevalence})}$$

As the PTPD depends largely on the pre-test probability of disease (i.e. the HCV prevalence in the population), Fagan's nomogram [29] was used to visualise the diagnostic gain after a PTA. This graphical calculation of Bayes' theorem describes how the result of a test (positive or negative) changes the perception of disease probability by combining the pre-test probability of disease with the likelihood ratio of the test (which is calculated from sensitivity and specificity) [28]. Fagan's nomogram converts pre-test probabilities into pre-test odds, then multiplies the odds by the likelihood ratios and converts post-test odds back to post-test probabilities. The PTPD was plotted for a range of HCV prevalences, including the prevalence in the liver disease patients, the estimated prevalence for the general Dutch population, and the prevalence expected to be revealed by the HCV internet programme.

We used SPSS for Windows (SPSS version 15.0, SPSS Inc., Chicago) and R (R version 2.7.1, libraries Epi and Binom; The R Foundation for Statistical Computing) to perform our statistical analyses.

Results

At the liver outpatient clinics, 99 patients filled out the core questionnaires anonymously while waiting for their consultation. In addition, 20 visitors at the National Hepatitis Week's patient symposium 2007 took part. Data on non-response for these two groups were not collected. Of the 459 members of the Dutch Liver Patient Organisation to whom the extended questionnaire was sent, 249 (54%) responded; 72 returned blank questionnaires, (some said they had not been tested for HCV and therefore could not participate; some did not want to); and 177 were willing to cooperate, yielding a response rate of 39% (177/459). In total, 296 patients took part: 99 and 20 filled out the core questionnaire (total 119), and 177 responded to the extended questionnaire.

One hundred and thirty-eight of the 296 participants (47%) reported that they were HCV-positive, 132 (45%) said they were HCV-negative, and 19 (6%) were unaware of their HCV status. An additional 7 (2%) did not give their HCV status and were therefore excluded, leaving 289 liver disease patients. Those unaware of their HCV status were assumed to be HCV-negative.

Table 2 shows characteristics and HCV risk factors of the liver disease patients by HCV status. As expected, prevalence of IDU, having received blood products before 1992, living together for >1 year and sharing bathroom items with HCV-infected individuals or IDU, having experienced a needlestick injury from a needle exposed to a high risk person, and non-injecting illicit drug use on regular basis were significantly higher among HCV-positives than among HCV-negatives. Being an organ recipient achieved borderline significance in the opposite direction (p=0.05). Prevalence of other risk factors did not differ significantly between HCV-positives and HCV-negatives, but the numbers of individuals with these exposures were often very small.

Sensitivity and specificity

Table 3 shows the sensitivity and specificity of both the core and extended HCV risk assessment questionnaires. Based upon the risk factors in the core questionnaire, 114 of 138 HCV-positive participants were identified as being at risk of HCV infection (PTA given), yielding a sensitivity of 82.6% (95% CI: 75.7 to 88.3). Of 151 HCV-negative participants, 96 were identified as not being at risk of HCV infection (NTA given), yielding a specificity of 63.6% (95% CI: 55.7 to 71.0). Stratified analyses and logistic regression analyses with sex and age as covariates and HCV testing advice (yes/no) as outcome variable, did not show significant differences in sensitivity or specificity by sex or age (data not shown).

The stability of our results was evaluated by excluding all cases (n=155) with missing values or uncertainties as to any risks or HCV status, yielding sensitivity of 85.9% (95% CI: 76.1 to 93.0) and specificity of 64.3% (95% CI: 52.7 to 74.9) (n=134, data not shown).

Finally, sensitivity and specificity were calculated for the extended questionnaire (including all risk factors

listed in table 1), yielding sensitivity and specificity of 84.6% (95% CI: 76.3 to 91.0) and 63.8% (95% CI: 52.9 to 73.7), respectively (n=171). With exclusion of all cases (n=86) with missing values to or uncertainties as to risks or HCV status, sensitivity was 89.4% (95% CI: 78.5 to 96.1) and specificity was 73.7% (95% CI: 58.4 to 85.8) (n=85, data not shown).

Table 2

Study population characteristics and identified HCV risk factors, HCV risk questionnaire evaluation study, the Netherlands, 2006-2007 (n=289)

Study population characteristics	Total number (%) n=289	HCV-positive number (%) n=138	HCV-negative/unknown number (%) n=151	p-value
Sex Male Female Unknown (missing)	 146 (51) 140 (48) 3 (1)	 69 (50) 68 (49) 1 (1)	 77 (51) 72 (48) 2 (1)	0.82
Educational level * Low Low-medium Medium-high High Unknown (missing)	 22 (8) 82 (28) 81 (28) 96 (33) 8 (3)	 5 (4) 42 (30) 35 (25) 52 (38) 4 (3)	 17 (11) 40 (26) 46 (30) 44 (29) 4 (3)	0.04
Median age in years*	50 (IQR=43-60)	53 (IQR=47-60)	47 (IQR=36-59)	<0.01
Born in the Netherlands *	201 (70)	105 (76)	96 (64)	0.02
Hepatitis B infection *	106 (37)	32 (23)	74 (49)	<0.01
HCV risk factors	Risk factor prevalence in study population			
IDU *	50 (17)	50 (36)	0	<0.01
Being born in a HCV-endemic country	1 (0.3)	1 (0.7)	0	0.48
Having received blood (products) before 1992 *	81 (28)	67 (49)	14 (9)	<0.01
HCV-infected mother	5 (2)	2 (1)	3 (2)	1.00
Mother is/was IDU	1 (0.3)	1 (0.7)	0	0.48
Living together for >1 year and sharing bathroom items with HCV-infected individuals *	20 (7)	14 (10)	6 (4)	0.04
Living together for >1 year and sharing bathroom items with IDU *	22 (8)	20 (14)	2 (1)	<0.01
Needlestick injury with needle exposed to high risk person (IDU, haemophiliac, dialysis patient, HCV-infected individual) *	23 (8)	21 (15)	2 (1)	<0.01
Needlestick injury in HCV-endemic country	1 (0.3)	1 (0.7)	0	0.48
Haemophilia patient	7 (2)	6 (4)	1 (0.7)	0.12
Haemodialysis patient	6 (2)	1 (0.7)	5 (3)	0.22
Organ recipient *	13 (4)	3 (2)	10 (7)	0.05
Having received blood (product) in medium/high risk country [a]	0	0	0	
Exposure of healthcare worker to blood/tissue in medium/high risk country[a]	6 (2)	2 (1)	4 (3)	0.69
Surgical/dental procedure in medium/high risk country[a]	15 (5)	7 (5)	8 (5)	0.93
Ritual intervention such as circumcision or scarification in medium/high risk country[a]	15 (5)	4 (3)	11 (7)	0.09
Tattoo in medium/high risk country [a]	6 (2)	2 (1)	4 (3)	0.69
Body-piercing in medium/high risk country[a]	3 (1)	1 (0.7)	2 (1)	1.00
HCV risk factors added in the extended HCV risk assessment questionnaire	total (n=171)	HCV positive (n=91)	HCV negative/unknown (n=80)	
HIV-positive status	5 (3)	2 (2)	3 (4)	0.67
NIDU ≥ 3 times a week for ≥3 months *	31 (18)	30 (33)	1 (1)	<0.01

CDC: United States Centers for Disease Control and Prevention; HCV: Hepatitis C virus; HDI: Human development index; HIV: Human immunodeficiency virus; IDU: Injecting drug user; IQR: Interquartile range; NIDU: Non-injecting illicit drug use; WHO: World Health Organization.

[a] Indicated as risk for HCV infection if happened in country with low or medium HDI or with an estimated HCV prevalence > 2% according to either WHO country-specific estimates [16] or CDC regional estimates [1].

* p<0.05.

In the extended questionnaire, HCV-positive patients were asked to describe their perceived route of infection. Fourteen HCV-positive participants (15.4%) had reported no risks and were therefore assigned to NTA. Nine of these 14 did not know how they acquired HCV; four presumed they had been infected due to:

Table 3

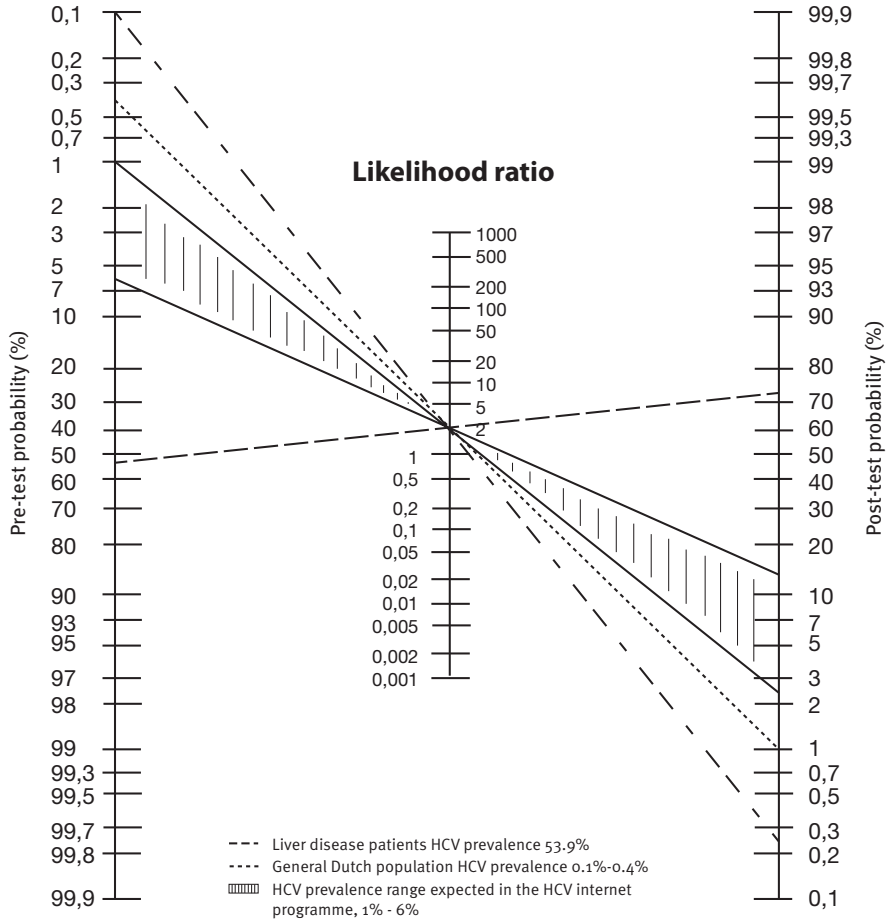
Relation between HCV risk questionnaire's advice and HCV status for core (n=289) and extended (n=171) versions of the questionnaire, HCV risk questionnaire evaluation study, the Netherlands, 2006-2007

	Core questionnaire			Extended questionnaire		
	HCV-positive	HCV-negative	Total	HCV-positive	HCV-negative	Total
Positive testing advice	114 (82.6%[a])	55 (36.4%)	**169**	77 (84.6%[a])	29 (36.3%)	**106**
Negative testing advice	24 (17.4%)	96 (63.6%[b])	**120**	14 (15.4%)	51 (63.8%[b])	**65**
Total	**138**	**151**	**289**	**91**	**80**	**171**

HCV: Hepatitis C virus.
[a] Sensitivity.
[b] Specificity.

Figure

Calculation of post-test probability of HCV, given positive testing advice, for liver disease patients and the general Dutch population and the HCV prevalence range expected in the HCV internet programme, HCV risk questionnaire evaluation study, the Netherlands, 2006-2007



HCV: Hepatitis C virus

dentistry, vaccination during military service, health care work without gloves, and travel vaccination in the mid 1970s. One HCV infection was officially recognised as occupational, resulting from police work related to traffic accidents.

Questionnaire validation

The sensitivity of the extended risk assessment questionnaire in the STI clinic patients was 90.0% (95% CI: 62.8 to 99.4) and its specificity 86.6% (95% CI: 84.3 to 88.6) (n=985). Sensitivity and specificity in the liver disease patients, ignoring risks about which the STI clinic patients were not asked, were 81.3% (95% CI: 72.5 to 88.4) and 77.5% (95% CI: 67.6 to 85.7) (n=171). The difference in sensitivity (8.7%) was not significant (p=0.69), but the specificity was significantly higher for the STI clinic patients (difference=9.1%, p=0.03).

Post-test probability of disease

The post-test probability of disease (PTPD) was calculated using sensitivity and specificity of the extended HCV risk assessment questionnaire in the liver disease patients. Fagan's nomogram (figure) shows the PTPD of a PTA and gives a precise view of diagnostic gain, specifically for low-prevalence populations. The line that starts at the left y-axis shows the pre-test probability of disease (i.e. the HCV prevalence), crosses the likelihood ratio for PTA (+LR, i.e. sensitivity/(1–specificity)), then points to the post-test probability of disease at the right y-axis. The diagnostic gain is the difference between the chance of disease for an individual before filling out the questionnaire (i.e. the prevalence) and the chance of disease for an individual after being assigned to PTA according to the questionnaire (i.e. the PTPD). For example, the diagnostic gain after PTA in the liver disease patients with a prevalence of 53.0% (n=171) is 19.5% (72.5% minus 53.0%), as shown by the striped line.

For the estimated prevalence in the general Dutch population (0.1%-0.4%[8]), the PTPD of a PTA is 0.23% to 0.93% (see dotted lines). The diagnostic gain varies from 0.13% (0.23% minus 0.1%) to 0.53% (0.93% minus 0.4%). In the HCV Internet programme, the media campaign, targeted at the general population, addresses risk factors for HCV and aims to refer those potentially at risk to the questionnaire. Therefore, we anticipate a prevalence of 1.0% to 6.0% in the population filling out the online questionnaire, yielding a PTPD of a PTA of 2.3% to 13.0% (vertically hatched area), which would lead to a diagnostic gain of 1.3% to 7.0%.

Discussion

Sensitivity was relatively high in this study. The HCV risk assessment questionnaire identified 84.3% of the HCV-infected individuals, and almost 90% when patients with missing values were excluded from analyses. In the STI clinic patients both sensitivity and specificity reached almost 90%. The fact that the risk assessment was based on self-reported risk factors, relying on the participant's memory instead of biological markers, strengthened the findings. Of the 14 HCV-infected individuals not identified by the questionnaire, only one mentioned a confirmed transmission route (police work related to traffic accidents). The others either did not know the route or mentioned various possibilities, such as dentistry, vaccinations, and health care work without gloves. Although all these possibilities include blood-blood contact and therefore could be sources of HCV infection, their probability of transmitting infection in low prevalence areas is likely to be very low. Furthermore, adding such risk factors to the questionnaire would decrease its discriminative value as it would lead to almost everyone in the Netherlands (or other low prevalence areas) being advised to seek testing.

The extended questionnaire performed better than the core questionnaire. It includes HIV as a risk factor for HCV. Recently, outbreaks of sexually acquired HCV infection have been reported among HIV-infected men who have sex with men [25]. Based largely on case studies, sexually-acquired HCV infection has been associated with HIV infection, the presence of ulcerative sexually transmitted diseases (STD), sexual practices that cause mucosal damage, and sex under the influence of drugs [25]. As the prevalence of HCV infection among HIV-infected individuals is high, partly because of shared bloodborne routes, and HCV/HIV co-infection accelerates HCV disease progression [30;31], HIV infection should be included in a HCV risk assessment questionnaire.

A few other studies have used or evaluated a risk assessment questionnaire for HCV infection [32-35]. For example, Lapane *et al.* found sensitivity and specificity of 69% and 74%, respectively, for risk factor based screening using a questionnaire including socially intrusive questions (e.g. IDU). Using this model, the costs per case detected were lower than when a questionnaire was used omitting socially intrusive questions, or when screening was based on elevated alanine transaminase levels [32]. However not all studies evaluated sensitivity, specificity, and feasibility in clinical practice. The feasibility of a pre-screening selection questionnaire, as opposed to mass screening, requires a balance between sensitivity and specificity, to ensure validity of the advice, diagnostic value, and cost-effectiveness of the selection method. The diagnostic value is largely dependent upon the disease prevalence. When the estimated prevalence in the general Dutch population (0.1%-0.4%) was used as a pre-test probability of disease, PTPD after PTA more than doubled but still remained small. This means that a large proportion of those who receive PTA will test HCV-negative, because of the relatively low risk of HCV infection associated with risk factors such as having received a blood transfusion. Nevertheless, false NTA is more problematic than false PTA because of the potentially severe long-term consequences of HCV infection. On the other hand, a large proportion

of HCV-negative individuals receive NTA and avoid the invasive and costly blood-screening procedure.

The following scenario illustrates the diagnostic value of the risk assessment questionnaire. If there is a population of 100,000 individuals, 2,000 of whom have HCV infection (prevalence 2.0%) and the aim is to trace them, one could simply test everyone, yielding one infected individual per 50 tested. Using a pre-screening selection questionnaire, however, 37,266 (84.6% of 2,000 HCV-infected plus 36.3% of 98,000 HCV-negative) individuals would be tested for HCV antibodies to trace 1,692 infected individuals, yielding a ratio of 1:22 instead of 1:50. Three hundred and eight (15.4% of 2,000) HCV-infected individuals would not be tested and therefore not traced, but 62,524 (63.8% of 98,000) HCV-negative individuals would not have to undergo testing. As the validation study showed a higher specificity in non-liver disease patients, the number of screened HCV-negative individuals may decrease when the questionnaire is applied to the general population.

Online use of the risk assessment questionnaire in the HCV internet programme appears feasible, and may be more cost-effective than other screening strategies, such as mass screening. Firstly, as the internet programme's public media campaign and website information will address risk factors (e.g. receiving a blood transfusion), the online questionnaire will be likely to attract groups at increased risk of HCV infection in the general population, leading to a higher PTPD after PTA. Secondly, the possible anxiety of HCV-negative participants who are concerned about their potential risk of HCV infection could be reduced by incorporating an internet-mediated, low-threshold, anonymous blood testing procedure (i.e. a service in which individuals print their laboratory forms from the website, visit a laboratory for blood sampling, and obtain their blood test results online). Thirdly, internet-mediated blood testing may reduce health care costs (e.g. GP consultations).

The internet may provide easy availability and anonymity, but certain factors must be considered when using the internet for offering an HCV risk assessment. Firstly, although internet uptake is high in the Netherlands, not all individuals have access to it or possess sufficient literacy or skills to use it. Secondly, it is a challenge to attract individuals to a website. Developing an HCV screening programme through the internet without marketing it properly would probably fail to identify HCV-infected individuals.

Our study has several limitations. We used self-reported HCV status of the liver disease patients to calculate sensitivity and specificity. Although unlikely in this population, it could be that some patients did not report their true HCV status. We did not collect data on non-response for the liver disease patients at the hospitals and at the symposium and were thus unable to evaluate whether selection bias had occurred. Our validation study made use of previously collected survey data. We cannot exclude the possibility that individuals who fill out a risk assessment questionnaire knowing its purpose (like the liver disease patients in our study) recall relevant information differently from those who take part in a survey without knowing why the data are being collected. A potential difference might result in an under- or overestimation of the sensitivity and specificity in our validation study. In general, we do not know whether our study population is representative for the population as a whole.

In conclusion, although our study population might not be representative for the population as a whole, the questionnaire's validity is high, as the testing advice agrees well with the HCV status in this study. The diagnostic gain, however, depends largely on HCV prevalence and is therefore lower when the questionnaire is used in low-prevalence populations.

We encourage the use of our questionnaire, especially in European countries where the prevalence is somewhat higher than in the Netherlands. A future study should assess the cost-effectiveness of a risk-based screening strategy in internet-based and alternative programmes compared with other strategies, such as mass screening or screening of easy-to-target-risk groups only (e.g. drug users who participate in care programmes). The cost-effectiveness analysis should take into account not only the prevention of future health care costs of identified HCV-infected individuals but also the health care costs associated with HCV-infected individuals who would not be detected using one of these screening strategies.

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CHAPTER 3.2

Using mass media and the Internet as tools to diagnose hepatitis C infections in the general population

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Using Mass Media and the Internet As Tools to Diagnose Hepatitis C Infections in the General Population

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Background: Many individuals with hepatitis C virus (HCV) infection are undiagnosed.

Purpose: This study describes the development and the use and outcomes of a mass media campaign, combined with an Internet risk assessment and an Internet-mediated blood-testing procedure for HCV to identify individuals infected with HCV in the general population.

Methods: From April 2007 to December 2008, individuals in HCV risk groups were referred to an online, previously validated risk-assessment questionnaire at www.heptest.nl. Individuals at risk could download a referral letter for a free, anonymous HCV blood test in a nonclinical setting. Test results could be obtained online, 1 week later, using a personal log-in code. Anti-HCV-positive participants were requested to visit the Public Health Service for confirmation and RNA testing. Chronically HCV-infected individuals were referred for treatment. Data were analyzed in 2009–2010.

Results: The website attracted 40,902 visitors. Of the 9653 who completed the questionnaire, 2553 were at risk for HCV (26.4%). Main reported risk factors were a blood transfusion prior to 1992 and noninjecting drug use. Of the 1480 eligible for the blood test, 420 opted for testing (28%). HCV antibodies were detected in 3.6% (n=15, 95% CI=2.1%, 5.7%); of the 12 with a chronic HCV infection, six began treatment.

Conclusions: Internet-mediated risk-based testing for HCV has proved to be a feasible and effective strategy to identify undiagnosed HCV infection in the general population. All HCV-infected individuals belonged to hard-to-reach populations. Test uptake was 28%, which is high for an online project that includes blood testing. Because Internet-mediated testing is low-cost, this strategy holds promise for future screening.

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Introduction

Hepatitis C virus (HCV) infection, caused by a blood-borne virus and first identified in 1989, is a major public health problem. Worldwide an estimated 123 million individuals are HCV antibody positive,[1] approximately 75% of whom are chronically infected and at risk for the development of cirrhosis, liver cancer, and death.[2,3] In chronically infected patients, the onset of HCV itself and the development of cirrhosis are usually asymptomatic.[2,4] Therefore, many infections remain undetected or are diagnosed late. On the basis of mathematical modeling, the HCV-related morbidity and mortality rates in high-income countries are expected to at least double in the next 2 decades.[5,6] Because successful combination therapy for HCV became widely available in

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2001[7–11] and an era of new therapeutic options is expected shortly,[12,13] the challenge now is to identify as many HCV-infected individuals as possible.

One option to meet this goal is a mass HCV screening program. Such a screening program in low-prevalence countries, however, is not considered cost effective.[14] As a result, mainly groups at high risk for HCV, such as current injecting drug users (IDUs),[15,16] and hemophiliacs,[17,18] have been targeted. In addition, as HCV spread among individuals who received contaminated blood products before the introduction of the first HCV antibody test in 1991, various high-income countries introduced look-back programs in which recipients of blood from HCV-infected donors were notified and encouraged to be tested.[19,20] The costs, however, were high, and the yield low.[21,22]

Attempts to identify HCV-infected individuals from multiple risk groups in the general population are scarce. A few studies have evaluated screening tools for determining risk of HCV (e.g., establishing individual risk for HCV infection as a condition for screening) to support efficient screening in healthcare facilities.[23–25] Such selective screening is promising and more affordable than mass screening,[26,27] but the use of these tools will not reach the pool of undiagnosed HCV-infected individuals who do not visit such facilities.

Therefore, wider distribution of screening tools for HCV risk is desirable. Use of the Internet has the potential to reach many individuals beyond the setting of healthcare facilities. For example, several studies have reported successful use of the Internet with screening programs for depression[28] and for syphilis in men who have sex with men.[29] In the Netherlands, because of the low HCV prevalence (estimated at 0.1%–0.4%[30,31]) and the widespread use of the Internet, HCV screening via the Internet could be feasible and effective. Therefore, a pilot project was developed and launched in two regions in the Netherlands. The project combined a mass media information campaign on HCV in the general population with an online risk-assessment tool and free blood-testing procedure for HCV. This paper describes the project and evaluates its usage, determinants of usage, and clinical outcomes.

Methods

Campaign Design

The project aimed to test inhabitants of Amsterdam (population size, 1,497,278) and South Limburg (population size, 608,885), the Netherlands, who were at risk for HCV. From April 2007 to December 2008, a limited, regional mass media campaign (e.g., with regional TV commercials, advertisements, and online banners) was run by the Public Health Services of Amsterdam and South Limburg. The campaign communicated risk factors for acquiring HCV, the fact that one can be infected without experiencing symptoms, the potential severe long-term health outcomes of chronic HCV, and the availability of treatment. The campaign aimed to motivate individuals to assess their risk for HCV using the project's website and then to be tested.

Risk-Assessment Procedure

The project website, accessible at www.heptest.nl and available in Dutch, English, French, Spanish, Turkish, and Arabic, contained information and a link to a questionnaire assessing HCV risk through structured multiple-choice questions that addressed the prominent risk factors for infection (Table 1). Risk factors were included if the expected prevalence in the specific group was considered to be high (on the basis of a theoretically plausible transmission risk, or epidemiologic data), or if not informing a specific group was considered to be unethical (e.g., individuals who were administered blood products before 1992 since they have never been informed in the

Table 1. HCV risk factors of individuals living in Amsterdam or South Limburg who were offered the blood-testing procedure, *n* (%)

Reported HCV risk	N=1480
Having received blood (products) prior to 1992	628 (42.4)
Non-injecting illicit drug use for ≥3 times a week during a period of ≥3 months	342 (23.1)
Medical/dental surgery in medium- to high-risk countries[a]	209 (14.1)
Living together for >1 year and sharing bathroom items with HCV-infected individuals or IDU	164 (11.1)
Ritual intervention such as a circumcision or scarification in medium- to high-risk countries[a]	141 (9.5)
Tattoo in medium- to high-risk countries[a]	134 (9.1)
Former IDU	62 (4.2)
Needle-stick injury with needle of high-risk people (IDU, hemophiliacs, dialysis patients, HCV-infected individuals)	41 (2.8)
Exposure of healthcare workers to blood/tissue in medium- to high- risk countries[a]	41 (2.8)
HCV-infected mother	40 (2.7)
Body-piercing in medium- to high-risk countries[a]	36 (2.4)
Being born in a HCV-endemic country	28 (1.9)
Having received blood (products) in medium- to high-risk countries[a]	14 (0.9)
Mother is/was IDU	12 (0.8)
Needle-stick injury in HCV-endemic countries	6 (0.4)

[a]Indicated as risk for HCV infection if in countries with low or medium Human Development Index (HDI) or with an estimated HCV prevalence >2% according to either country-specific estimates of the WHO[34] or regional estimates of the CDC[1]

HCV, hepatitis C virus; IDU, injecting drug user

Netherlands). In addition, to exclude individuals already diagnosed with HCV infection from the testing, data regarding results of possible previous HCV tests were collected. In addition, questions were included to inform uninsured individuals about their need for health insurance to receive HCV treatment in the Netherlands.

Individuals who reported at least one risk factor for HCV were advised to have a blood test. Individuals in the risk groups that are regularly tested for HCV in the pilot regions (i.e., those receiving hemodialysis or organ transplant, hemophiliacs, HIV-infected individuals, and active IDUs participating in drug-user healthcare programs) were advised to visit their general practitioner or specialist for testing and were discouraged from using the Internet-mediated testing procedure. All other individuals living in the pilot regions who were at risk for HCV were offered the free, anonymous HCV blood test, whereas those living outside the pilot regions were advised to visit their general practitioner for testing. The diagnostic accuracy of the risk-assessment questionnaire was previously examined, yielding a sensitivity of 84.6% and specificity of 63.8%.[32]

Blood Test

The project's website provided a referral letter to a testing laboratory, along with instructions and addresses of the participating laboratories. All but one of the laboratories were walk-in laboratories, mainly used by primary care professionals as referral facilities. Each referral letter carried a unique identifying code generated by the computer. Participants could print, download, or send the referral letter to an e-mail address. They also could opt to receive either an e-mail or short message service (SMS) reminder, subscribe to an alert service, or both. Those who chose a form of reminder received a message to be tested 5 days later.

After the participants presented the referral letter to the laboratory, they had their blood drawn for serologic testing by a third-generation commercial microparticle enzyme immunoassay (MEIA) system (AxSym HCV, version 3.0; Abbott). The test results were uploaded online, where participants could obtain their results using their unique identifying code. Those subscribed to the alert service received an automated message when their results were uploaded. Individuals who tested positive were informed about a potential HCV infection and were requested to visit the Public Health Service again for HCV antibody, recombinant immunoblot assay, and HCV RNA testing (AxSym HCV, version 3.0; Chiron RIBA HCV 3.0 SIA, Ortho-Clinical Diagnostics; Cobas Amplicor, Roche, respectively). Participants who were found to be chronically infected with HCV were referred to a hepatologist. Informed consent was obtained for notifying the participant's general practitioner and for future HCV clinical data collection. The medical ethics committee of the Academic Medical Center, Amsterdam, decided that the project did not require IRB approval.

Measures

Website usage and user characteristics. Website visitors were counted via the total number of website hits. The chosen website language and the Internet provider (IP) address (i.e., a code identifying a specific computer on the Internet) were recorded. Further, the questionnaire included data on sociodemographics (age, gender, educational level), postal codes, and whether individuals who completed the questionnaire intended to assess their risk for HCV or just out of curiosity. The last is also referred to as a "seriousness check,"[33] enabling the exclusion of nonintentional website users (e.g., other researchers who wanted to just review the questionnaire) from the evaluation analyses. In the analyses, those individuals were excluded, as well as those who previously tested positive for HCV and risk groups who were presumed to have already undergone testing and were therefore discouraged from using the questionnaire and blood-testing procedure. The collected data were used to assess the proportion and characteristics of website users at risk for HCV, as well as determinants for risk of HCV.

Use of hepatitis C virus blood test. Among those individuals determined to be at risk for HCV, the proportion that underwent the blood test was assessed, with the subsequent results. Of those who tested positive, the proportion that visited the Public Health Service for follow-up testing was assessed. To examine determinants of blood testing, data were used from the questionnaire and the subscriptions to the reminder service.

Clinical outcomes. The number of individuals identified as HCV-antibody-positive, and the proportion of chronically infected (HCV–RNA positive) individuals were measured, and data were collected on treatment and outcomes.

Statistical Analyses

Descriptive analyses were used to assess the characteristics of the website users. With logistic regression analyses, determinants of being at risk for HCV and determinants of using the HCV blood test among those eligible for testing were examined. Variables evaluated in the analyses included sociodemographics and whether an individual had health insurance. Age was categorized based on quartiles. Educational level was divided into four categories (low: primary school; low-medium: lower secondary school; medium-high: senior secondary school/vocational school; high: higher vocational education/University/PhD). In the second analysis, the proximity of the nearest laboratory (celestial latitude based on midpoints of postal-code areas categorized by quartiles), reminder-service subscription, and specific HCV risks were also evaluated. Participants who reported more than one HCV risk were allocated to the group that included the most likely risk factor for HCV. The results in Table 2 are presented according to this hierarchy.

Variables with a p-value of ≤ 0.10 in univariate analyses were entered in the multivariate logistic regression model. A stepwise backward selection procedure was used. A p-value of ≤ 0.05 was considered significant. In sensitivity analyses, potential duplicate cases, which were defined as participants who reported the same gender, date of birth, postal code, country of birth, and the same IP address, were included only once at their last participation date.

SPSS for Windows, version 17.0, and Stata statistical package, version 9.1, were used for statistical analyses. Data were collected from March 2007 to December 2008, and the analyses were performed in 2009 and 2010.

Results

Website Usage

From March 2007 to December 2008, the website attracted 40,902 visitors (Figure 1). Of that number, 38.5% started the risk-assessment questionnaire and completed the seriousness check. According to that check, 15.7% did not intend to determine their risk for

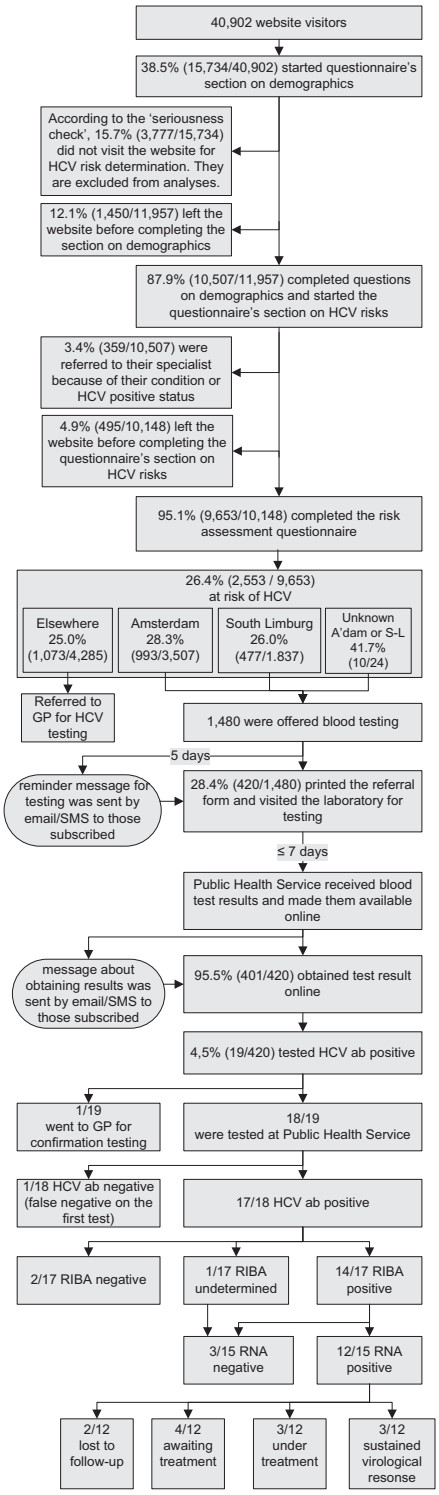
Table 2. Univariate and multivariate logistic regression analyses of factors associated with HCV testing among participants at risk for HCV (N=1480)

		Univariate		Multivariate	
Characteristics	**HCV tested (%)**	**OR (95% CI)**	***p*-value**	**Adjusted OR (95% CI)**	***p*-value**
Age (years)			<0.001		<0.001
<32	55/392 (14.0)	1		1	
32–45	91/373 (24.4)	2.0 (1.4, 2.9)		1.5 (1.02, 2.3)	
46–54	127/363 (35.0)	3.3 (2.3, 4.7)		2.6 (1.7, 3.8)	
>54	146/345 (42.3)	4.5 (3.1, 6.4)		3.4 (2.3, 5.2)	
Missing	1/7 (14.3)	—		—	
Gender			<0.001		
Male	156/659 (23.7)	1		—	
Female	264/821 (32.2)	1.5 (1.2, 1.9)		—	
Educational level			0.023		0.003
Low	48/180 (26.7)	1		1	
Low-medium	113/463 (24.4)	0.9 (0.6, 1.3)		1.1 (0.7, 1.7)	
Medium-high	164/499 (32.9)	1.3 (0.9, 2.0)		1.9 (1.2, 2.9)	
High	46/143 (32.2)	1.3 (0.8, 2.1)		1.8 (1.0, 3.0)	
No answer	49/195 (25.1)	0.9 (0.6, 1.5)		1.2 (0.7, 2.1)	
Country of birth					
Netherlands	327/1155 (28.3)	1		—	
Elsewhere	93/325 (28.6)	1.0 (0.8, 1.3)		—	
Region of residence			0.008		0.046
Amsterdam	262/993 (26.4)	1		1	
South Limburg	158/477 (33.1)	1.4 (1.1, 1.8)		1.4 (1.01, 1.9)	
Unknown whether in Amsterdam or South Limburg	0/10 (0)	—		—	
	—	—		—	
Proximity of the nearest laboratory (km)			0.003		0.003
<1.17	106/319 (33.2)	1		1	
1.17–2.19	113/384 (29.4)	0.8 (0.6, 1.2)		0.9 (0.6, 1.3)	
2.20–6.08	109/364 (29.9)	0.9 (0.6, 1.2)		0.7 (0.5, 1.0)	
>6.08	89/362 (24.6)	0.7 (0.5, 0.9)		0.5 (0.4, 0.8)	
Unknown (incomplete postal code)	3/51 (5.9)	0.1 (0.0, 0.4)		0.2 (0.1, 0.8)	
Health insurance			0.102		0.028
Insured	404/1440 (28.1)	1		1	
No/unknown about insurance	16/40 (40.0)	1.7 (0.9, 3.3)		2.4 (1.1, 5.2)	
Request for e-mail/SMS reminder			<0.001		<0.001
No	352/1342 (26.2)	1		1	
Yes	68/138 (49.3)	2.7 (1.9, 3.9)		2.8 (1.9, 4.1)	
HCV risk group			<0.001		<0.001
Blood transfusion prior to 1992	204/545 (37.4)	1		1	
Having lived together with HCV-infected/IDU and having shared bathroom attributes	27/92 (29.3)	0.7 (0.4, 1.1)		0.8 (0.5, 1.4)	
	10/29 (34.5)	0.9 (0.4, 1.9)		1.3 (0.6, 3.1)	
Mother HCV-infected/IDU	6/23 (26.1)	0.6 (0.2, 1.5)		0.7 (0.3, 2.0)	
Needle-stick injury	103/396 (26.0)	0.6 (0.4, 0.8)		0.9 (0.6, 1.2)	
Risky event in medium-/high-risk country	34/306 (11.1)	0.2 (0.1, 0.3)		0.3 (0.2, 0.5)	
NIDU on a regular basis	12/27 (44.4)	1.3 (0.6, 2.9)		1.8 (0.8, 4.4)	
HCV endemic country of birth	24/62 (38.7)	1.1 (0.6, 1.8)		1.1 (0.6, 2.0)	
Former IDU	—	—		—	

Note: ORs in the multivariate model are adjusted for all factors for which adjusted ORs are shown: age; educational level; region of residence; proximity of the nearest laboratory; health insurance; request for e-mail/SMS reminder; HCV risk group.
HCV, hepatitis C virus; IDU, injecting drug user; NIDU, non-injecting drug user; SMS, short message service

HCV and were excluded from further analyses. Of the remainder, 12.1% left the website before completing the questionnaire's section on demographics; 87.9% completed the demographics and began the questions regarding risk factors for HCV.

Of the 10,507 who began the risk factor section of the questionnaire, 0.7% indicated that they had tested positive for HCV before, and 2.7% belonged to the specific risk groups presumed to have received previous testing for HCV. These individuals were discouraged from fur-



ther participation, referred to their specialist, and excluded from additional analyses.

Of the remaining 10,148, only 4.9% left the website before completing all questions, whereas 95.1% completed the questionnaire, 5368 of whom were living within the referral regions for the blood test. Of those, 51.5% were female. The median age was 38 years (interquartile range [IQR]=26–50 years). The education level varied from low (10.2%) to low-medium (30.3%); medium-high (38.5%); and high (9.5%); whereas 11.6% refused to answer this question. Most individuals (86.6%) were born in the Netherlands; 5.4% were born in another Western country, and 8.0% were of non-Western origin. Only 1.3% used a version of the questionnaire in a language other than Dutch, and 27.6% appeared to be at risk for HCV. In multivariate analyses, being at risk for HCV was associated with female gender (OR=1.3, 95% CI=1.2, 1.5); having a low-medium (OR=1.2, 95% CI=1.1, 1.4) or unknown educational level (OR=1.3, 95% CI=1.04, 1.6) compared with a medium-high educational level; older age (OR=1.3, 95% CI=1.1, 1.6, for those aged 27–38 years; OR=2.3, 95% CI=1.9, 2.7, for those aged 39–50 years; OR=3.0, 95% CI=2.5, 3.6, for those aged >50 years; all compared with those aged <27 years); being born outside the Netherlands (OR=2.5, 95% CI=2.1, 3.0); and not having health insurance (OR=1.8, 95% CI=1.2, 2.8) (data not shown). In the sensitivity analysis, excluding potential duplicate participants (n=172), results were comparable.

Hepatitis C Virus Blood Testing and Its Determinants

The blood test was offered to those at risk living within the referral regions. Table 1 shows an overview of the reported HCV risks of these individuals. Of the 1480 participants, 19.7% reported more than one risk factor. In total, 28.4% opted for testing. The median time between website visit and their testing was 5 days (IQR=2–10), and most individuals were tested within 3 weeks after their website visit.

Table 2 shows the results of univariate and multivariate analyses of determinants of HCV testing. In the sensitivity analysis, excluding potential duplicate participants (n=70), results were comparable.

Figure 1. Overview of the Internet procedure, usage, and clinical outcomes
A'dam, Amsterdam; GP, general practitioner; HCV, hepatitis C virus; RIBA, ribavirin; S-L, South Limburg; SMS, short message service

Clinical Outcomes

Of the 420 who tested, only 4.5% did not obtain their test results from the website (all tested negative for HCV antibody), and 4.5% (95% CI=2.8%, 6.8%) tested positive for HCV antibody. All but one individual visited the Public Health Service for confirmation testing; that person stated he preferred to visit his general practitioner for that testing. In the analysis, that person was considered to be positive for HCV antibody. Twelve individuals were chronically infected with HCV, of whom 11 reported former injecting drug use (IDU), and one reported a blood transfusion prior to 1992. The lower portion of Figure 1 shows an overview of the clinical outcomes of these individuals.

Discussion

To our knowledge, this is the first time a public HCV information campaign targeting the general population has been launched combined with risk-based blood screening for HCV via the Internet.

This study shows that the online process of assessing risk, arranging a blood test, and obtaining the results is feasible. The blood-test uptake of 28% is high; a similar, successful online method of testing for syphilis yielded a test uptake of 10%.[29] Further, almost all of those who were tested for HCV through the project obtained their results online, and all individuals with positive results went to their general practitioner or Public Health Service for confirmation testing.

The project's strategy succeeded in identifying HCV-infected individuals in the general population, resulting in a HCV prevalence of 3.6%, which is nine to 36 times the estimated prevalence in the general Dutch population (0.1%–0.4%[30]). Most of those identified with chronic HCV infection were former IDUs not taking part in the present healthcare services for IDUs. Hence, it is unlikely that they would have been identified without the current project. Considering the high prevalence in this group, interventions are needed to both reach and inform former IDUs, as well as to motivate them to be tested.

The volume of the project's reach was limited; in a period of 21 months, it attracted 1480 individuals at risk for HCV living in the pilot regions. This small number is attributed to the restricted reach of a regional media campaign. Toward the end of the project, a 1-day national media event was arranged, and an immediate peak in exposure and testing was observed, far exceeding all peaks during the regional campaign (data not shown). Therefore, in future similar efforts, it is recommended that national media be used to achieve the maximal exposure needed to reach hidden populations for HCV. Further, the proportion of non-Western migrants participating in the project (8.0%) was lower than expected, based on the proportion of those living in the pilot regions (12.7%; Statistics Netherlands, 2009). Given the importance of reaching these groups because of their presumably higher risk for HCV, an additional, more-direct approach is suggested, such as through organized outreach activities supported by community leaders.

Regarding determinants of HCV testing, individuals of older age, of higher educational level, and with residence in a less urbanized region were more likely to be tested. Older age and higher educational level have been associated previously, but not consistently, with screening uptake for various diseases.[35] The higher uptake of HCV screening in less-urbanized South Limburg compared to Amsterdam is also observed in the age-corrected uptakes for cancer screening in these regions.[36] Explanations might include small regional differences in the media campaign, or a potential perception of a higher level of authority of the local Public Health Service.

Further, not having health insurance was associated with being tested. In the Netherlands, individuals without a residence permit are uninsured; hence, they do not have access to regular health care. Because HCV testing in the online project was not restricted to those having health insurance, it may have created a specific health gain for the uninsured group that otherwise might not have been feasible.

Also, NIDUs were less likely to test compared with the other risk groups. Because the reported HCV prevalence in NIDUs varies between 2.3% and 35.3%,[37] it is suggested that future screening programs make more effort to motivate this group for testing. The geographic distance to the testing location was found to be associated with testing, indicating that screening projects should minimize the travel distance to the laboratory, for example, by organizing a mobile testing unit. Also, reminder messages were found to stimulate testing behavior. As shown in other studies,[38,39] reminder messages can be an effective and relatively easily implemented strategy to increase test uptake in screening projects, especially with computer-based methods.

Regarding study limitations, the analyses are based on the individuals who responded to the campaign and used the website and thus do not give insight into the total population at risk of HCV in the study regions. This limits the generalizability of the findings. In addition, the reach of the media campaign was not measured. Further, it is unknown whether participants at risk who were not tested through the project decided to be tested elsewhere. If participants have been tested elsewhere, the impact of the program has been underestimated.

Conclusion

The online approach proved to be feasible and effective in identifying undiagnosed HCV-infected individuals in the general population. It may be used for screening for other diseases, recognizing that its impact can be increased with a more extensive mass media campaign combined with direct outreach approaches for immigrant risk groups. Online testing offers many advantages, such as low cost and anonymity. It should be complementary to regular screening options, especially in countries with high prevalence of Internet use. Proximate testing locations and reminder messages are important in enhancing the effectiveness of screening projects that involve collection of body specimens.

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CHAPTER 3.3

Reasons for compliance or noncompliance with advice to test for hepatitis C via an Internet-mediated blood screening service: a qualitative study

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Reasons for compliance or noncompliance with advice to test for hepatitis C via an internet-mediated blood screening service: a qualitative study

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Abstract

Background: Hepatitis C virus (HCV) is mainly transmitted by exposure to infected blood, and can lead to liver cirrhosis and liver cancer. Since the onset of HCV and the development of liver cirrhosis usually are asymptomatic, many HCV-infected individuals are still undiagnosed. To identify individuals infected with HCV in the general population, a low threshold, internet-mediated blood testing service was set up. We performed a qualitative study examining reasons for compliance and noncompliance with advice to test for HCV via the online blood testing service.

Methods: Semistructured telephone interviews were conducted with 33 website visitors who had been advised to test for HCV (18 testers, 15 non-testers). Transcribed interviews were analyzed qualitatively and interpreted using psychosocial theories of health behavior.

Results: Reasons for testing pertaining to the online service were: the testing procedure is autonomous, personalized test advice is provided online, reminder emails are sent, and there is an online planning tool. Reasons for testing not specific to the online service were: knowing one's status can prevent liver disease and further transmission of HCV, HCV is curable, testing can provide reassurance, physical complaints are present, and there is liver disease in one's social environment. Service-related reasons for not testing pertained to inconvenient testing facilities, a lack of commitment due to the low threshold character of the service, computer/printing problems, and incorrectly interpreting an online planning tool. The reasons for not testing that are not specific to the online service were: the belief that personal risk is low, the absence of symptoms, low perceived urgency for testing and treatment, fear of the consequences of a positive test result, avoiding threatening information, and a discouraging social environment.

Conclusions: Features specific to the online service played a significant role in motivation to test for HCV above and beyond the more conventional perceived health benefits of HCV testing. However, some online specific features were considered problematic and need to be adapted. Methods and strategies for dealing with these impeding factors and for improving compliance with testing via the online service are outlined.

Background

Hepatitis C virus (HCV) infection, caused by a blood-borne virus and first identified in 1989, is a major public health problem. Worldwide an estimated 123 million individuals are HCV antibody positive, [1] approximately 75% of whom are chronically infected and at risk for the development of cirrhosis, liver cancer, and death [2,3]. In chronically infected patients, the onset of HCV itself and the development of cirrhosis are usually asymptomatic [2,4]. Therefore, many infections remain undetected or are diagnosed late. On the basis of mathematical modeling, the HCV-related morbidity and mortality rates in high-income countries are expected to at least double in the next 2 decades [5,6]. Because successful combination therapy for HCV became widely available in 2001 [7-11] and an era of new therapeutic

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options is expected shortly [12,13], the challenge now is to identify as many HCV-infected individuals as possible. Consequently, the Public Health Services of Amsterdam and South Limburg introduced the Hepatitis C Internet Project, a pilot study aimed at identifying undiagnosed HCV-infected individuals in the general population.

In the Netherlands, the estimated HCV prevalence is low (0.1-0.4% [14]). Therefore, the strategy used in the Hepatitis C Internet Project consisted of a public media campaign that addressed HCV risk factors and referred risk groups to an online HCV risk assessment questionnaire at http://www.heptest.nl[15]. Individuals who visited the website and were identified by the questionnaire as at risk were advised to get tested for HCV and were immediately offered the opportunity to arrange, online, a free and anonymous HCV blood test. The website also provided information about HCV risks that was tailored to the individual's risk profile and emphasized the severity of HCV infection, its often asymptomatic onset, and the benefits of treatment. It also explained the testing procedures, stating that the blood test procedure included an initial HCV antibody test, a follow-up test for those who tested positive, and a direct referral to the hospital for those infected with HCV. Individuals could arrange the blood test themselves by printing out a laboratory form that contained a personal identification code with which participants could anonymously obtain their test result online seven days after testing. The form also included addresses and opening hours of the participating low threshold test locations. In order to increase the test uptake, individuals were offered an online planning tool for testing where they could specify the date, time, and location upon which they would have their blood drawn for the HCV test. The tool explicitly mentioned that it did not result in an actual appointment with the laboratory and that individuals later could decide to take their test at a different date, time, or location. The tool was considered advantageous because, according to the theory of Implementation Intentions [16], detailed planning of when and how to execute an intended action facilitates the actual performance of the behavior. In addition, individuals could subscribe to an email and/or a mobile phone Short Message Service (SMS) reminder system if they wanted to receive a reminder message for blood testing five days after they completed the risk assessment questionnaire.

While 28% (n = 420) of the individuals who completed the risk assessment questionnaire and were found to be at risk for HCV infection (n = 1,480) complied with the test advice and were tested for HCV, a substantial proportion (72%) failed to visit the test locations. Because the online testing service is new, it is unclear which service-related factors promoted or impeded website visitors' decision to test for HCV. Understanding why some complied with the advice to test through the online service and others did not is vital to not only the further implementation of this service but also to the improvement of HCV testing campaigns in general. Therefore, this study investigated reasons for compliance and noncompliance with the HCV test advice obtained through the online risk screening tool and focused particularly on the role of the online blood testing procedures in that process. A descriptive qualitative design was used to be able to explore and understand the participants' views and motives with regard to HCV testing.

Theoretical background

The health belief model [17,18], the theory of planned behavior [19], and the extended parallel process model [20] were used as theoretical bases for the interpretation of the findings. The health belief model focuses on perceived severity of and vulnerability to a disease (perceived threat), perceived barriers to and benefits of executing the behavior (expectations regarding the outcomes of the positive health behavior), perceived self efficacy (the degree to which one perceives oneself capable of executing the health behavior), and cues to action (stimuli which trigger the cognitive processes that lead to the health behavior). Applied to the context of HCV screening, the likelihood of HCV testing increases when perceived threat of HCV is high, perceived barriers of testing are low, perceived benefits of testing are high, self efficacy for testing is high, and relevant cues for action are present.

The theory of planned behavior suggests that behavior is determined by more than just health beliefs. According to the theory of planned behavior, attitudes (personal evaluations of the behavior based on behavioral beliefs), subjective norms (perceptions of other people's evaluations of the behavior based on normative beliefs), and behavioral control (perceived control over the execution of the behavior based on control beliefs; similar to self-efficacy) determine the intention to engage in a behavior. Behavioral intention is presumed to best predict behavior. However, actual behavioral control (e.g. lack of control due to environmental factors) can also directly influence behavior. Applied to the context of HCV screening, the likelihood of HCV testing increases when attitudes towards testing are positive, when subjective norms favor HCV testing, and when perceived behavioral control is high.

The extended parallel process model also focuses on health beliefs but is more specific than the health belief model with regard to the role of emotion in responses to a perceived health threat. According to the extended

parallel process model, health threats can cause individuals to engage in either danger control or fear control processes. Danger control is aimed at reducing the health threat through cognitively processed adaptive responses (e.g. seeking testing and treatment), whereas fear control is aimed at reducing unpleasant feeling related to the health threat. Fear control often results in maladaptive responses such as message avoidance and defensive reactions (e.g. denial of risk). Whether individuals engage in danger or fear control processes depends on the degree to which threat, self efficacy, and response efficacy (the extent to which the recommended behavior is expected to effectively reduce the threat) are perceived to be present [20]. Medium to high perceived threat combined with high perceived efficacy will most likely result in danger control responses while high perceived threat combined with low perceived efficacy will most likely lead to fear control responses. In a study conducted with men who have sex with men (MSM) by Mikolajczak et al. [21], men at risk for HIV mentioned both the fear of testing HIV-positive and a low perceived risk of HIV infection as reasons for not testing, thus implying that cognitive dissonance reduction takes place. Applied to the context of HCV screening, the extended parallel process model would suggest that the likelihood of HCV testing is greatest when individuals perceive the threat of HCV as moderate to high and possess high levels of perceived self efficacy and response efficacy.

Methods

Recruitment and Sample

Because the Hepatitis C Internet Project was anonymous, only individuals who had subscribed to the reminder service could be contacted for participation in this study. To note, those who subscribed to the service were informed that they could receive an email invitation for participation in a study. Recruitment took place among these individuals between May and July 2007 and between May and July 2008 (n = 97). The invitation sent by email briefly explained the study procedures and indicated that the aim of the study was to improve the project by hearing the opinions of participants. The invitation was sent at least three weeks after the potential participant's website visit, in order to provide the participant with sufficient time to be tested, but no later than three months, in order to reduce potential recall bias. If individuals did not reply to the email invitation within two weeks, an email reminder was sent. Recruitment of participants continued until data saturation [22] was reached, i.e. until no new reasons for compliance or noncompliance emerged from three consecutive interviews. In total, 33 interviews were conducted. Information regarding demographics (sex, level of education, and country of birth) and HCV risk factors were obtained from the online risk assessment questionnaire data. Age was asked during the interview.

Procedure

Semistructured interviews were chosen as they allow flexibility, facilitate empathy, enable the interview to explore new topics, and tend to produce rich data [23]. Interviews were conducted in Dutch by telephone. Telephone interviews were considered the most ideal choice as they lower possible barriers to participation (e.g. travelling to the Public Health Service) and enhance anonymity. Two female researchers conducted interviews of approximately 15 minutes each. Every interview commenced by explaining the purpose of the interview followed by an oral informed consent. The following topics were then addressed: motives for visiting http://www.heptest.nl and filling out the risk assessment questionnaire; feelings about the outcome of the risk assessment; personal perception of risk for HCV infection (this topic was added after the first two interviews); and the reasons for compliance or noncompliance with the advice to test for HCV. The central topic of the interview concerned why participants used or did not use the project's testing service. Follow-up probes (e.g., "Could you explain this further?") were applied to motivate participants to provide a detailed rationale for their test decision. All interviews were audio-taped and transcribed verbatim (quotes are translated). Participants were provided with a gift certificate as reward for their participation.

Analyses

The transcribed interviews were entered into a database for coding and content analysis using qualitative data analysis software (MAXqda 2007). The data analysis team consisted of four researchers from different disciplines (communication science, biomedical science, psychology, and anthropology). The data analysis consisted of two phases; in the first phase the data were analysed in an inductive manner, not informed by the theoretical frameworks. In the second phase, the results of the first phase were interpreted using the theoretical frameworks. A detailed description of the two phases follows below.

Phase 1: After conducting the first two interviews, two researchers independently coded those interviews. In order to stay as close as possible to the phenomenon described by the participants, coding was inductive and open, not yet classified or interpreted through the theoretical frameworks, and an unrestricted number of facets were expressed in preliminary code names. A discussion meeting with the data analysis team then took place to ensure that all relevant content was incorporated in codes. Furthermore, based on the first two interviews,

the team discussed whether additions were needed to the initial interview schedule. Thereafter, two additional interviews were conducted and discussed. This iterative process of interviewing alternated with open coding and a team discussion comprised three rounds. Thereafter, when all 33 transcripts were coded, the team reached consensus on the final code names. The codes had to be concise and self-explaining. If multiple codes were found that refer to a similar principle (e.g., the codes: 'inconvenient opening hours of the laboratories', 'no evening opening hours', and 'needing an appointment for a specific time to be tested at the closest laboratory'), codes were merged together (in this example into 'inconvenient test facilities'), reducing the number of codes. Consequently, the first author then reread the coded segments of the 33 transcripts to confirm that all coded segments fitted in the final code names.

Phase 2: Focusing on the research question, the team then grouped the relevant codes into categories based on the theoretical background of the health belief model, the theory of planned behavior, and the extended parallel process model. Each category was based on at least one code.

Ethical framework

Prior to the interviews, participants were informed about the purpose of the interview and the fact that they could withdraw from participation whenever they wished (also after finishing the interview), by emailing the researcher that had contacted them via email previously (none of the participants withdrew). Oral informed consent for audio taping the interview was requested before the interview started. To maximize confidentiality, potential personal identifiers were deleted from the transcripts, and only the involved researchers had access to the interview transcripts. The study was approved by the Ethical Committee Psychology of the School of Psychology and Neuroscience, Maastricht University.

Results

Sample characteristics

Most participants (91%; 30/33) were born in the Netherlands and female (79%; 26/33). Median age at the time of the interview was 49 years (IQR = 41-62 years). Educational level varied from low (22%) to moderate (19%) to high (59%). Of the 33 participants, 18 (55%) had complied with the test advice and had used the project's testing service. One of these 18 had tested positive for HCV. The participants belonged to various HCV risk groups. The most frequently reported risk was having had a blood transfusion before 1992 (n = 16), followed by having the skin pierced in countries with medium to high HCV prevalence (n = 13). Other reported risks were former injecting drug use (n = 2), frequent use of non-injection illicit drugs (i.e., cocaine, heroine, amphetamine, LSD, GHB and/or poppers; n = 1) and living together and sharing bathroom attributes with HCV positive individuals or drug users (n = 4). Three participants had multiple HCV risks.

Reasons for testing related to the online testing procedures

From the interviews with participants that had been compliant with the advice to test (N = 18), we identified five reasons for testing that related directly to the online testing procedure (see upper right section of Figure 1). The first reason was that the online testing service allowed individuals access to a test without having to discuss or explain their desire to be tested for HCV with their general practitioner (GP). This reason was labeled '*to avoid the GP*' and is illustrated by the following quotes:

> "At that time [years ago], I thought about testing but I didn't do it. [...] The reason is that, back then, you had to visit the GP - it was the standard procedure - and you'd have to tell him or her why you want a test [...] and, with this offer, you can remain anonymous but still get tested." (tester [T]-8)
>
> "I have a lot of health problems. Visits to the GP are time-consuming and, above all, you don't want to be thought of as a whiner. [...] Everytime you have something, you kind of start to dislike to yourself and, by bringing it up with the GP, it's like you are again make a big deal out of things." (T-9)

The second reason for compliance pertaining to the testing service was that the online service enabled users to become well-informed about HCV and the testing procedures without time pressure and at their own pace. The fact that participants '*could obtain information independently*' enabled them to deliberate about whether or not they should test for HCV:

> "Well, after doing the risk test and being told that I need to test, then you can search for information yourself and find out what it all means, you know? Then you are not blindly having your blood drawn while you actually know nothing. You can immediately search on the internet. You can look up why or how and what... Then I think, 'It's not so scary, I'll do it'" (T-1).

The third reason was that there was '*personalized test advice*'. The tailored feedback on risk factors provided motivation to test, as illustrated by the following quote:

> "Well it [the personal advice] is so clear that you feel compelled to follow the advice you receive" (T-8).

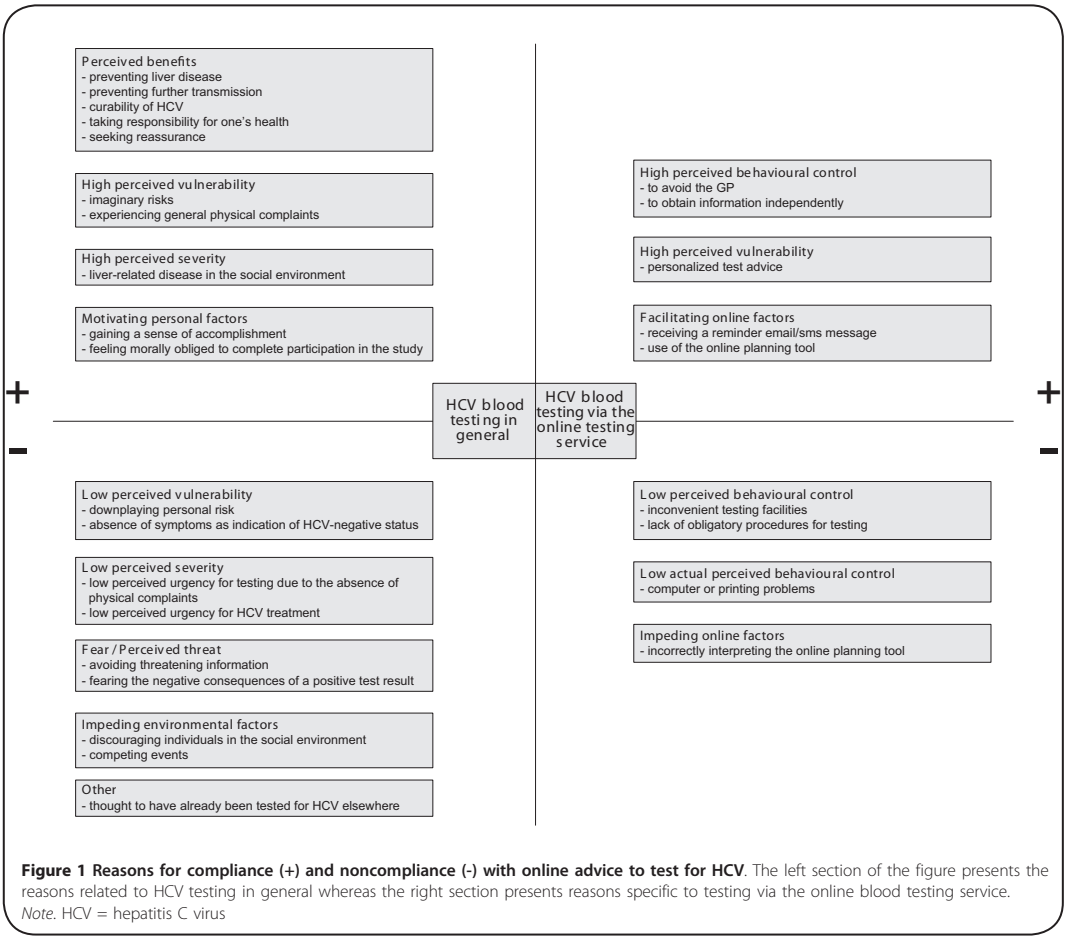

Figure 1 Reasons for compliance (+) and noncompliance (-) with online advice to test for HCV. The left section of the figure presents the reasons related to HCV testing in general whereas the right section presents reasons specific to testing via the online blood testing service. *Note.* HCV = hepatitis C virus

The fourth reason was that participants had been reminded to get tested. '*Receiving a reminder e-mail/ sms message*' alerted individuals to the test advice and promoted testing, as illustrated by the following the quote:

> "Well, actually, I think if I didn't get that reminder of yours, it would have ended up in the back of my mind, like something I would have to do some time. [...] Without the reminder, I probably wouldn't have gotten tested." (T-12)

The final reason for compliance related to the online service was the availability of the online planning tool. The '*use of the online planning tool*' stimulated participants to test:

> "I think it's a helpful tool. They ask you what date you want to go. I thought, 'Hey, that's good. I'll just pick that date. I'll do it. I'll just put it in my day-planner and I'll do it'" (T-7).

Reasons for testing unrelated to the online testing service

We identified ten reasons for testing that were unrelated to the online testing service (see upper left section of Figure 1). First, participants mentioned health gain from early detection of HCV. This was labeled as '*preventing liver disease*' and is illustrated by the following quote:

> "These diseases always start small. They are invisible and, later on, they develop further and, at a certain point, you're too late for treatment. You know, it gives you problems. If you find it at an early stage, you may be able to cure or treat it." (T-4)

Secondly, participants reported testing because the undetected virus could spread to other people. This reason was labeled as '*preventing further transmission*' and is illustrated by the following quote:

> "I thought, 'Well, for goodness' sake, let me get the test.' [...] also because I could infect others with it" (T-7).

A third reason for testing was labeled '*curability of HCV*'. This reason focused on the fact that there are treatment options for HCV when diagnosed. One participant said,

> "I also read that there are medications and stuff available, so I thought ooohkay. [...] I thought, 'Well, this is not very scary, I will do it.' You get me?" (T-1).
> Another participant stated, "I heard that if you have it, it can be effectively treated, at least if you've detected it at an early stage. That's why I reacted immediately" (T-6).

Furthermore, some participants expressed that caring for one's own health and body was imperative. '*Taking responsibility for one's health*' was thus one of the reasons to test for HCV:

> "Look, when I hear about something like this, I take action immediately. It is my body and I believe that we should care for our bodies. And when you are offered something like this, well, then you should do it" (T-18).

Some participants mentioned that they got tested because they wanted to know their HCV status. They were not scared of the test results but reported that they were '*seeking reassurance*':

> "I wasn't afraid that something was wrong but, yes, I wanted to be sure." (T-5); and "I have other things, I mean unpleasant things [medical conditions] so I liked being able to exclude something" (T-9).

Several participants had incorrect perceptions regarding HCV risks. They had experienced certain events that they considered to pose a risk. Although these events posed no actual risk, they did increase perceived risk and motivated individuals to test. We labeled this reason as '*imaginary risks*':

> "I've had numerous medical examinations and much more. I've had a stroke, three TIAs. [...] I used to go for walk in wooded areas and I've been bitten by ticks [...] so I thought, "Oh, oh maybe it [being HCV positive] could be because of all that." (T-2)

Also, some participants reported testing because they were '*experiencing general physical complaints*'. One participant said the following:

> "It said that you could be carrier for a long time and that it won't manifest itself - only maybe in a much later stage - that it can take years. And yes, well maybe it's because lately I have had a lot of complaints that I never had before. I thought well, 'For goodness' sake, let me get the test.'" (T-7)

In addition, knowing people with liver-related diseases was mentioned as a reason for testing. This was labeled as '*liver-related disease in the social environment*' and is illustrated by the following quote:

> "At this time, I have acquaintances who are dying because of their liver. So I think the liver is very important" (T-18).

Another reason for testing was based on the principle of finishing what you started and was labeled as '*gaining a sense of accomplishment*':

> "Well, I tested because I think, 'Well, I want to know, finish this, just do it.'" (T-17).
> "There was no specific, no special reason, just to have it done" (T-11).

Finally, some participants tested in the interest of science or in the interest of the organization facilitating the testing. This reason was labeled '*feeling morally obliged to complete participation in the study*' and is illustrated by the following quotes:

> "If everyone starts but, for whatever reason, doesn't finish, that doesn't bring any good to science or [knowledge] dissemination or anyone. So I thought, 'Let me be the person who does do it.'" (T-12).
> "I found it nice to know that people are doing this [providing HCV testing]. It gives you the sense that you also need to reciprocate so it won't be one-sided" (T-17).

Reasons for not testing related to the online testing procedures

From the interviews with participants who did not comply with the test advice, we identified four reasons for not testing related to the online testing service (see lower right section of Figure 1). The first reason reported was that specific features of the laboratories (e. g. opening hours) hindered them from getting tested. This reason was labeled as '*inconvenient testing facilities*' and is illustrated by the following quotes:

> "The laboratory which is closest to me is open until, I believe, half past one or half past two [...] and it didn't get to the point that I thought, "Let's go out of bed early to get the test." (non-tester [NT]-15).

> "The one that is closest to me - there you can only test by appointment and then I thought, 'Well, I may be in another area someday where there is a lab that doesn't work with appointments and then I'll just walk in to have blood drawn.' That's just more convenient." (NT-6).

Second, the test procedures did not engage participants to commit to taking the test immediately but rather allowed for testing until the end of the year. The testing procedure had therefore an optional, facultative character. This reason was labeled as '*lack of obligatory procedures for testing*' and is illustrated by the following quotes:

> "Because I am a diabetic, I have to get blood drawn pretty often, and I thought 'Well, this can wait a little while.' I will certainly do it in time, before December. And that's the deadline you determined" (NT-9).
> "I think, for these kind of things, I kind of really need to be ordered to come. It should say, 'Well, on this day at that particular time, you should be there.' Then I would probably free up time for it" (NT-7).

Third, some participants reported '*computer/printing problems*' as a reason for not testing:

> "I went to print the form to have the test and my printer broke. It didn't work anymore and I don't have a new printer yet" (NT-11).
> "My computer broke down and then I actually didn't end up doing anything with it" (NT-12).

Finally, we found that incorrectly thinking that the online planning tool was a real appointment planner caused uncertainty as to whether the test could still be taken when the planned appointment was skipped. In this situation, we found '*incorrectly interpreting the online planning tool*' to be a reason for not getting tested:

> "Well, I skipped the appointment and I didn't know whether I could go another time so I thought, 'Well, then I need to visit my own GP'" (NT-5).

Reasons for not testing unrelated to the online testing service

We identified eight reasons for not testing that were unrelated to the online testing service (see lower left section of Figure 1). First, despite the results of their online risk assessment, some participants felt they were not at risk or downplayed their reported personal risk for HCV. This reason was labeled as a '*downplaying personal risk*':

> "Actually, I naturally assumed that when you receive blood in the hospital, it's fine" (NT-16).
> "I got a tattoo in South Africa but, from what I can remember about that tattoo shop, it was hygienic and they always used new needles. At the time, I never had the sense and today I still don't have the sense that I got something, hepatitis C or maybe something else that you can get from unhygienic tattooing." (NT-15)

Second, some participants perceived the likelihood of being HCV-infected as low because they did not have HCV-related symptoms. The '*absence of HCV symptoms as an indication of HCV-negative status*' is illustrated by the following quote:

> "Otherwise I would be completely yellow now. In any event, I don't have any symptoms" (NT-10).

Third, some participants mentioned that there was no immediate need to test as they were not suffering from physical distress that disrupted their daily lives. This reason for not testing does not reflect the perception that one is not at risk but rather it reflects a perceived lack of immediate need to test that is rooted in the perception that the potential HCV infection is not a handicap to the participant's daily functioning. The argument '*low perceived urgency for testing due to the absence of physical complaints*' is illustrated by the following quote:

> "I don't have any physical complaints now, regardless of whether or not I have it. There's no emergency. [...] And because now I have little, actually, no complaints, it is not on the top of my priority list. It is not something I really have to do." (NT-15).

We also found that some participants perceived that there was little to be gained from diagnosing and treating a long-term persisting infection now instead of later, and therefore postponed testing. The '*low perceived urgency for HCV treatment*' is illustrated by the following:

> "It is not something that is life-threatening. It is not like if I don't get treated within a month, I will be dead by next month. You know, because it is such a long time ago" (NT-8).

Furthermore, some participants reported rejecting the test advice in order to prevent emotional worries about being infected. This was labeled as '*avoiding threatening*

information' and is illustrated as follows:

> "I always think that you shouldn't always take everything to heart because, if you do, you'll feel it yourself too. I always try to be very straight in that. When I have a headache, I don't think, 'Well then, I will probably also have this and that.' [...] It [not seeking testing] is because of that. We shouldn't take everything to heart." (T-11).

In addition, '*fearing the negative consequences of a positive test result*' and the corresponding uncertainty regarding the chain of events following a positive test result was also an impediment to testing:

> "Is taking the medication hard? Are you stuck with it for the rest of your life? What is it? What are the risks? I don't have a clue. And imagine that the test result is positive. Then you think, "What am I getting myself into?" (NT-6).
> "It is just like [...] pretending it isn't there [...] burying your head in the sand. [...] I just have to, how can I say it, I have to get the courage to take that step. [...] Yes, because imagine that it is not good, you would have never taken that into account." (NT-9).

Some participants mentioned '*discouraging individuals in the social environment*' as a reason for not testing, as illustrated by the following:

> "I didn't go and get the test yet because my husband says, 'Well, you don't have to do it.' [...] My children also took a look at the laboratory form and questioned whether it was necessary. [...] Actually, in the beginning, I thought I'd go to the Public Health Service and because other people saw it [the form] and said to me, 'Oh, you don't need to do it,' that's why I haven't done it yet." (NT-13).

Also, '*competing events*' were found to impede testing for HCV, as illustrated by the following quote:

> "Unexpectedly, my father had surgery so I am always at the hospital and I haven't been able to do anything for myself. So I haven't tested yet because of these private matters." (NT-8).

Finally, some participants '*thought they had already been tested for HCV elsewhere*' and therefore did not get tested again:

> "Yes, I wanted to do the test but my GP had already sent me for extensive blood work because, lately, I haven't been feeling well. Then it turned out that my blood had been tested for almost everything and the results showed that my blood was okay." (NT-3)

Reasons for intention to test among noncompliant participants

Without explicit solicitation, the majority (11/15) of the participants who did not comply with the test advice expressed the intention to get tested in the future. One reason was the '*ease of testing*':

> "Actually I assume that I'm not infected. That's what plays a role but, because it is that easy, I think, 'Well let's then do it just to be sure'" (NT-6).

Another reason is the '*anonymity of the testing service*' as illustrated by the following quote:

> "Where I live - a small village - if you got to the local care unit where blood is drawn, you see all sorts of people you know. If you sit there, then you're either pregnant or you have some scary disease. Well for me, I don't like that, so I'd prefer to go to Amsterdam." (NT-5).

Both of the above-mentioned reasons for intention to test are comparable to reasons for testing mentioned by the compliant participants.

Participants with the intention to test also mentioned reasons related to the benefits of testing. Again, these were identical to those mentioned by the compliant participants. These were '*preventing of liver disease*': "I think everything is okay but there is a chance that I have it. So then maybe it is just better to know and maybe go through nasty treatment for a while so that I don't have complaints later on." (NT-15); '*curability of HCV*': "Well if you read that if you're infected, it is possible to get treated, then I think, 'Well, maybe I should find that out'" (NT-6); '*seeking reassurance*': "Yes, I intend to test just to know for sure that it's not there" (NT-13); and '*preventing the further transmission of HVC*': "Yes, well, I have four children so [...] I have another responsibility too. If I were to get sick then I could also infect my children" (NT-5).

Discussion

The purpose of this study was to gain a better understanding of, firstly, why some people who receive online advice to test for HCV comply with that advice while others do not and, secondly, the role of the online testing procedures in compliance and noncompliance with testing advice. Here, we discuss our findings in relation to existing theory. We suggest methods and strategies to

improve not only our online HCV screening project but also other comparable projects that use online tools or aim to encourage individuals to test for HCV.

We found that the autonomous nature of the testing procedure (i.e. with this procedure, it is possible to obtain information independently and to get the test without having to discuss it with a GP) motivated individuals to go for testing. From the theoretical perspective of the theory of planned behavior, the autonomous nature of the service increases perceived behavioral control over the testing procedure as it removes constraining conditions (e.g. having to discuss testing with a GP). The autonomous nature of the service clearly illustrates the added value of internet-based screening projects complementary to existing prevention and screening options. In future screening projects, the autonomous nature of the testing procedure should to serve as the strongest selling-point in communication about the service.

Furthermore, we found that getting an HCV test was also motivated by the fact that knowing one's HCV status can provide reassurance for those who test negative, and can prevent liver disease and inhibit the further transmission of HCV through the initiation of treatment and precautionary measures for those who test positive. Also, knowing that HCV is curable promotes testing. From the perspective of the health belief model, these reasons reflect the expected benefits of testing that can be obtained from either a positive test result followed by treatment and preventive measures or a negative test result (reassurance). We suggest that screening projects communicate not only the physical gains of testing positive but also the emotional benefits that testing negative can potentially offer to especially individuals in low prevalence populations.

As expected, high perceived severity of HCV and high perceived vulnerability to HCV motivated individuals to seek testing. High perceived severity was based on experiences with liver disease in the social environment, where seeing significant others suffer from liver disease increased the will to prevent the disease. High perceived vulnerability was mainly based on the personal test advice that was tailored to the individual's risk profile. The positive effect of tailored health information on screening uptake has been demonstrated previously. For example, Skinner et al. found that among groups with low adherence to breast cancer screening (African American and low-income women), a mammography recommendation letter that was tailored to women's specific health belief model perceptions resulted in a higher mammography adherence at follow-up compared to those who received a nontailored version of the letter [24]. Both perceived vulnerability and severity fit the health belief model, in which especially high perceived vulnerability is an important predictor of performing a desired health behavior [17]. Among the participants in our study, however, sometimes strong feelings of vulnerability were based on previously experiences or events that do not carry any risk for acquiring HCV or on physical complaints unrelated to HCV. For these individuals, the project's threatening information likely created excessive worry that, in turn, motivated testing. Although it was the project's aim to motivate individuals at risk for HCV to seek testing, this finding indicated that presenting threatening information may also motivate the 'worried well' to seek testing. We suggest that HCV screening campaigns increase the perceived relevance of testing for those at risk while also seeking to mitigate the worried well response. This could be done by presenting information about potential personal risk for HCV together with information about the issues that might cause individuals to needlessly worry about HCV (e.g. risks related to other less severe infections).

Furthermore, we found that some individuals got tested to gain a sense of accomplishment and a sense of personal gratification from getting the test that could be interpreted as an anticipated positive emotional reaction. Others claimed to have a moral obligation to complete their participation in the study, which appears to be a form of altruism. Other studies have shown that altruism can indeed motivate participation in research and other projects [e.g. [25]]. Screening projects could use the argument of anticipated gratification in persuasive communication that seeks to enhance compliance with test procedures (e.g. in a reminder message).

Reminder messages and the online planning tool were indicated by some users as facilitative of testing. Reminder messages can be described best as cues to action. They help individuals to recall their initial motivation and rationale to test. The effect of reminders has been demonstrated previously, for example by Sequist et al [26], who showed that colorectal cancer screening rates were higher for patients who received mailings compared with those who did not, and DeFrank et al [27], who showed that reminders were effective in promoting repeat mammography adherence. In our project, we used relatively simple reminder messages that simply stated that individuals should seek testing. The impact of these reminders could likely be improved by including messages that play into the established reasons for testing (e.g. the benefits of testing or the anticipated gratification of finishing the testing procedure).

The online planning tool that was offered to individuals after their online risk assessment supported individuals to set their testing goal and to plan each step toward that goal. This module assisted in closing the gap between intention and behavior and its effect has previously been demonstrated [28]. However, in our

study, some individuals did not go for testing because they mistook the online planning tool to be a real appointment planner and, once the planned appointment was missed, they felt uncomfortable making a new appointment. Alternatively, they thought that they could only test at their initially chosen location and time. We suggest that future online planning tools include a clearer explanation of its self-regulating nature in order to prevent the incorrect perception that the planning tool is a real appointment planner. It would also be advantageous to inform those who miss their planned test date that it is possible to get the test at another moment in time. In addition, online planning tools could incorporate email or SMS reminder messages that, for example, a day prior to the planned appointment, send a reminder message in which the personal goal (i.e. getting tested at a particular date, location, and time) is reiterated.

With respect to the reported reasons for not using the online HCV testing service, we found that the lack of obligatory procedures for testing and inconvenient testing facilities impeded testing. Although these aspects reflect the autonomous nature of the testing service, which did motivate most individuals to seek testing, some found these very same features to be barriers to their use of the service. Individuals had to plan the HCV testing appointment themselves and the online service did not incorporate any procedures that produce high commitment for testing (e.g. scheduling real appointments). Moreover, the online testing procedure unintentionally offered a cue for procrastination as it explicitly indicated a lenient deadline for testing (i.e. a maximum of 12 months). We suggest that online screening projects in the future provide individuals with a clearly defined and relatively tight deadline for testing. We recommend a period of one month as the evaluation study of the HCV internet project (data not published) showed that most individuals were tested within two weeks.

Furthermore, we found that low perceived urgency for testing and treatment impeded testing for HCV. From the perspective of the health belief model, this reason reflects low perceived severity of HCV infection which can lead to procrastination in testing. Although it is true that, in most cases, HCV is not an acute life-threatening disease that demands immediate treatment, individuals cannot precisely know the degree to which their (potential) infection has progressed. We thus suggest that future HCV screening projects emphasize this and seek to deter the notion that HCV treatment can be easily postponed. This could be done by outlining both the negative consequences of postponing an HCV test and the benefits of immediate testing and subsequent treatment.

Additional reasons for noncompliance with HCV test advice were that no symptoms were present and that the risk was downplayed. These reflect low perceived vulnerability of HCV infection. The absence of symptoms as an indication that no infection has occurred might be based on a false belief that all HCV infections are accompanied by physical symptoms. Interestingly, the information provided by the testing service did indicate that the majority of HCV infections are asymptomatic. The fact that individuals mentioned these reasons for not testing despite the provision of appropriate information and personalized advice to seek testing may reflect unrealistic optimism, which is an optimistic bias regarding personal vulnerability to a health threat ["It won't happen to me"; [29]]. With this in mind, we suggest the use of scenario-based risk information that addresses doubts about personal risks and the consequences of downplaying of risk. For example, future efforts to promote compliance with test advice could use the story of a HCV-infected peer who was diagnosed late because he did not experience any symptoms and thought that his chance of having acquired HCV was small.

Although low perceived severity and vulnerability (representing low perceived threat) can lead to procrastination or noncompliance with testing advice, we should be careful with respect to increasing perceived threat as we found that some individuals showed testing avoidance because of a high perceived threat. For these individuals, avoidance of threatening information and fear of the consequences of a possible positive test result impeded testing. As such, the advice to seek testing may have resulted in a fear control reaction as described by the extended parallel process model. According to this model, high perceived threat in combination with low perceived efficacy for testing can lead to maladaptive responses such as denial of the message and message avoidance. Therefore, screening projects should not only seek to address personal risk and increase the perceived health threat of HCV; they should also endeavor to increase individuals' perceived response and self efficacy for managing a possible infection. In our project, we informed individuals about the blood testing procedure but we did not specifically mention the face-to-face post-test counseling session with a trained professional that always follows a positive test result. We, therefore, recommend that screening projects provide more detail on the procedures that follow a positive test result. Online screening projects could also incorporate opportunities for an immediate online post-test counseling session (e.g. via webcam) in addition to face-to-face counseling. Furthermore, they could include an online module that teaches individuals the necessary skills to overcome their fear of a positive test result by, for example, arranging support from family members.

Some participants indicated that individuals in their direct social environment discouraged them from testing for HCV. According to the theory of planned behavior, a strong negative subjective norm (i.e. others' beliefs regarding testing plus the motivation to comply with the beliefs of others) can influence testing behavior. In order to overcome social pressure not to test, screening projects can offer skill-building tools that help individuals to negotiate or withstand discouragement from their environment. Scenarios that offer counterarguments against a discouraging partner or demonstrate how to surpass social pressure and maintain the original testing intention would be beneficial in this regard.

Some participants reported a malfunctioning computer or printer as a barrier to testing. In our project, individuals could have their laboratory form emailed to them or they could download it onto their computer but we did not actively offer individuals a solution to printing problems. This technical problem could be overcome in future screening projects by offering to send the laboratory form by post or by having the laboratory forms emailed to mobile phones or to the laboratories directly.

Finally, competing events impeded testing. Most of the reported competing events were very serious (e.g. hospitalization of a family member). Consequently, the low prioritization of HCV testing by these participants seems reasonable. Given this finding, we suggest that future HCV screening projects incorporate a multiple reminder system in which individuals are reminded of testing not only a couple of days after their risk assessment, as in our project, but also a couple of weeks later.

Although our study focused on reasons for compliance and noncompliance with advice to test for HCV, some noncompliant participants mentioned that they still intended to test. These participants provided similar reasons for testing as the advice-compliant participants. This suggests that the reasons for testing and the reasons for not testing may have played a role in both testers' and non-testers' decision-making. It would be interesting to further investigate what discriminates individuals who eventually test from those who do not. It could be that testers encountered the impeding factors to a lower extent or that they overcame these factors better than non-testers. Quantitative studies in the future could provide further insight regarding the presence and strength of the various reasons among both groups and their relation to testing.

To our knowledge, this is the first study to explore reasons for compliance and noncompliance with an HCV test advice in the general population. Previous studies have been conducted among drug users [30-32]. In these studies, some of the reasons for testing or not testing for HCV were similar to those identified by our study. For example, these studies also found that a motivating factor is that the test enables avoidance of the GP and an impeding factor is low perceived risk of being infected. However, the drug users in these studies rarely mentioned reasons for testing related to health benefits. They also mentioned many dissimilar reasons for noncompliance such as fear of needles, perceived lack of confidentiality regarding test results, and fear of discrimination and stigmatization. This seems to suggest that HCV testing projects targeting active drug users should have a different focus (e.g. focus on issues relevant to drug users' lifestyles and competing problems) than HCV testing projects targeting the general population.

Our study has a number of limitations. First, the participants were individuals who had responded to a HCV campaign, completed the online risk assessment questionnaire, and left their email address. Individuals who did not respond to the campaign or who left the website before completing the risk assessment questionnaire were not invited to participate. This could generate a selection bias whereby our study sample includes relatively more individuals who were informed and committed to the service. Also, women and individuals of Dutch origin dominated the study sample and not all risk groups for HCV were represented (e.g. individuals born to an HCV-positive mother). Future research should focus on the reasons for (non-)participation of these groups.

Conclusions

This study has shown that our online screening campaign motivated individuals to test because the testing service is autonomous, because tailored risk information is provided, because a reminder message service is in place, and because there is an online planning tool. Furthermore, our study elicited a number of feasible intervention targets to improve the uptake of HCV testing in general. We suggest that HCV screening projects include a deadline for testing and anticipate the responses of individuals with low perceived risk for HCV by, for example, raising awareness of personal risk and outlining the consequences of not testing. Also, projects could communicate the emotional benefits of testing negative in addition to the physical gains of testing positive. Furthermore, projects could provide additional insight regarding the procedures that follow a positive test result. We propose that organizing an effective low threshold HCV testing procedure for the general population could not have been successful without the internet. Given its tailoring capabilities, flexibility, and the relatively low costs, the internet is a promising tool not only for arranging HCV testing but also for motivating individuals to get tested by providing them with advice based on a personal risk profile. In addition,

we believe that the anonymous character of the internet and subsequent testing procedures are especially helpful for addressing stigmatized diseases like HCV.

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Authors' contributions
FRZ coordinated the study, carried out the interviews, participated in the data analyses and interpretation, and drafted the manuscript. TRLJH participated in the data analyses and interpretation, and contributed to the drafting of the manuscript. ATU carried out the interviews and participated in the data analyses, and contributed to the drafting of the manuscript. MP contributed to the study design, the interpretation of the results, and drafting of the manuscript. GK contributed to the interpretation of the results and drafting of the manuscript. UD conceived and supervised the study and analyses, and led the writing. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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CHAPTER 4

COMMUNITY OUTREACH TO PROMOTE HEPATITIS B AND C SCREENING

CHAPTER 4.1

Screening for hepatitis B and C in first-generation Egyptian migrants living in the Netherlands

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Abstract

Background: Egypt has high prevalence of hepatitis C virus (HCV) infection and intermediate prevalence of hepatitis B virus (HBV) infection; however, infection prevalence among Egyptian migrants is unknown. Considering the asymptomatic onset and development of disease in chronically-infected patients, many may remain undiagnosed.

Aims: To evaluate a screening programme designed to identify undetected HCV and HBV infections among first-generation Egyptian migrants in Amsterdam, the Netherlands.

Methods: In 2009 and 2010, viral hepatitis educational and screening sessions were established at Egyptian meeting places. Data regarding demographics and risk factors for HCV infection were collected. Chronically infected participants were referred and followed up. Phylogenetic analyses were used to ascertain the geographic origin of infections.

Results: Eleven of 465 (2.4%; 95%CI=1.3-4.2%) migrants had anti-HCV antibodies; 10/11 were HCV RNA positive. All had HCV genotype 4a infection, and strains were typical of those of Egypt and the Middle East. Older age and exposure to parenteral antischistosomal therapy (PAT) were significantly associated with HCV infection. Anti-HBc prevalence was 16.8% (95%CI=13.7-20.4%); HBsAg prevalence was 1.1% (95%CI=0.5-2.5%). All had HBV genotype D infection, typical of those of the Middle East. Most (9/10 HCV; 3/5 HBV) chronic infections were newly diagnosed; four of the HCV-infected individuals started treatment.

Conclusions: Anti-HCV and HBsAg infection prevalence among Egyptian migrants was lower compared with the general Egyptian population, but higher than the general population of Western countries. Phylogenetic analyses suggest that all infections were from the region of origin. Screening programmes for HCV infection should target first-generation Egyptian migrants, especially those of older age and those who received PAT, and include screening for HBV infection.

Introduction

Infections with hepatitis B virus (HBV) and hepatitis C virus (HCV) affect an estimated 2 billion [1] and 123 million [2] people worldwide, respectively. The majority of HCV infections and the minority of HBV infections progress to chronic infection, placing the patient at risk for the development of cirrhosis, liver cancer, and death. Three quarters of liver cancers worldwide are attributed to chronic HBV and HCV infections [3]. Because of their asymptomatic course, chronic HBV and HCV infections often go undetected and infection may be identified long after exposure.

The country with the highest estimated prevalence of HCV infection worldwide is Egypt. Because of the use of contaminated injection material in large-scale parenteral antischistosomal therapy (PAT) campaigns from the 1920s to the 1980s, nearly 15% of the general Egyptian population has been infected [4]. In contrast, in the general population of the United States and many Western European countries, the HCV antibody prevalence, even in urban areas with a diverse population, is estimated below 2% [5-8]. The use of contaminated injection material in PAT campaigns probably also lead to an increase in the reservoir for HBV infection in the general Egyptian population [9], and the HBsAg prevalence has been estimated at 2 to 7% [10].

Starting in the 1960s, political, economic, and social developments led Egyptians to migrate to the Arab Gulf, Europe, and North America. According to Egyptian government statistics, 2.7 million Egyptians live abroad; 1.9 million in the Arab Gulf, 430 thousand in North America, and nearly 400 thousand in Western Europe [11]. Little is known, however, about the prevalence of HCV and HBV infections among Egyptian migrants living in high-income countries. Considering the fact that the PAT campaigns started long before the 1960s and subsequent migration, an appreciable number of Egyptian migrants may be infected with HCV. Many who have been infected may remain undiagnosed, since the onset of HCV infection and disease progression often are asymptomatic. Treatment options for chronic HCV infection have improved substantially over recent years [12]. Thus, the identification of HCV- and HBV-infected Egyptian migrants can significantly improve prognosis, reduce disease morbidity and mortality, and prevent further transmission.

In 2009 and 2010, a community-based screening programme for first-generation Egyptian migrants was established in Amsterdam, the Netherlands, to identify those who were infected with HCV, to refer them for care, and to investigate the prevalence and determinants of HCV infection. Since treatment options for chronic HBV infection have improved [13], and Egyptians are at increased risk, the programme also included screening for HBV infection. Phylogenetic analyses were used to investigate the origin of HCV and HBV infections in Egyptian migrants. The study results aimed to inform future screening policies for HCV and HBV infections in migrants.

Materials and methods

Recruitment

An estimated 20,000 Egyptians have migrated to the Netherlands [14], of whom approximately 3,200 are 18 years of age and older and live in the region of Amsterdam [15]. In 2009, we searched the internet for Egyptian organizations in the greater Amsterdam area, and contacted all identified organizations: a Coptic church, two Islamic mosques, an Egyptian women's empowerment organization, an Egyptian trade organization, a weekend school for Islamic Egyptians, and an Egyptian supermarket.

From September 2009 until September 2010, with the support of key figures within these organizations (e.g., the imam, priest, chairperson, owner of the supermarket), we organized 11 viral hepatitis educational and screening sessions, usually planned after regular meetings of each organization. The key figures distributed invitations for the sessions to their members/customers using our promotion flyers. We distributed approximately 1500 flyers to the community organizations. These flyers informed about transmission routes and risk factors for hepatitis A (HAV), B and C infections, vaccination against HBV infection, the consequences of unrecognized HBV and HCV infections, the fact that screening was free of cost during this campaign for those born in Egypt, and the availability of treatment. For customers of the Egyptian supermarket, the session was organized at the local public health service. Egyptians who were unable to attend a session were invited to visit the Public Health Service of Amsterdam for screening by appointment. The medical ethics committee of the Academic Medical Center, Amsterdam, decided that the project did not require IRB approval.

Screening procedure

The educational sessions were held in standard Arabic by Arab educators who were trained on the subject of viral hepatitis. They addressed the risk, transmission routes, prevention, consequences, and treatment options for chronic HBV and HCV infections. After the session, all adults (18 years and older) were offered screening for HBV and HCV infections. Those who opted for screening were given an information package, available in Dutch and Arabic, including information on the project, an informed consent, and a questionnaire on risk factors for HCV infection. Filling out the questionnaire was optional. After reading the information and filling out the forms, trained healthcare workers performed venipuncture to collect blood. Blood specimens were transported to and processed in the laboratory of the Public Health Service of Amsterdam.

Laboratory testing

HCV serological testing was done by third-generation commercial microparticle EIA system (AxSym HCV version 3.0; Abbott) and confirmed by recombinant immunoblot assay (Chiron RIBA HCV 3.0 SIA, Ortho-Clinical Diagnostics). Samples positive for anti-HCV were further tested for HCV RNA by transcription-mediated amplification (TMA; Versant®, Siemens). For HBV, the blood samples were first tested for anti-HBc using microparticle enzyme immunoassay (AxSYM CORE TM, Abbott). When positive or indeterminate, HBsAg was determined (AxSYM HBsAg version 2.0, Abbott, confirmed with a neutralization test [miniVidas, Biomerieux]).

Sequencing and phylogenetic analyses

HCV RNA and HBV DNA in the samples that tested positive for HCV RNA and HBsAg, respectively, was isolated, amplified, and sequenced, using an in-house PCR as described previously [16;17]. HCV and HBV sequence data have been deposited in the GenBank sequence database under accession numbers JN564679-JN564688, and JX489382-JX489386, respectively. The viral genotypes for HCV and HBV infection were determined after phylogenetic analysis of the sequences obtained, along with established GenBank reference sequences [18].

Phylogenetic comparisons for the HCV and HBV sequences was made as previously described by Van de Laar et al. [19] and Van Houdt et al. [17], respectively. The HCV sequences of Egyptian migrants from this study were compared to those obtained from HCV genotype 4-infected patients previously diagnosed in the Netherlands including Egyptian migrants and injecting drug users [19-21], as well as to sequences from HCV genotype 4-infected drug users and patients originating from the Middle East that were obtained from the Los Alamos database [22]. The HBV sequences of Egyptian

migrants from this study were compared to those obtained from drug users, men who have sex with men, and reported cases of acute HBV infection including migrants from the Middle East who were diagnosed in the Netherlands [17;23;24].

Follow-up procedure

Participants who tested negative or had cleared their infection received their test results within 3 weeks by postal mail. Those found to be chronically infected with HBV and/or HCV were sent a letter requesting them to call the Public Health Service so that they could be orally informed of their test results. Those chronically infected with HCV were invited for a consultation with a visiting hepatologist at the Public Health Service of Amsterdam, at which the test results and possible treatment options were discussed, and referral to a hospital was arranged. Those chronically infected with HBV were referred to their general practitioner (GP) for further diagnostics. In addition, in accordance with the Dutch Public Health Act, the department of infectious diseases of the public health service in a patient's home town was notified, a contact tracing procedure was initiated, and susceptible contacts were vaccinated. Participants who tested anti-HBc negative were advised to get vaccinated against HBV infection when travelling to Egypt. The GPs of all participants were informed about the test results.

Measures

Questionnaire

The questionnaire that was given to those who opted for screening consisted of questions addressing the following risk factors for HCV infection: schistosomiasis treatment with injections and/or pills; blood transfusions; surgical operations; injections; dental surgery; hemophilia; hemodialysis; organ donors; hospitalizations; circumcision; hijamas (i.e., a traditional Arab treatment, in which blood is drawn by vacuum from a small skin incision); acupuncture treatment; needle stick incidents; non-injection drug use; injection drug use; tattoos; piercings; and whether participants had family members with HCV infection. For all risk factors except having HCV-infected family members, we asked the calendar year and country in which the risk factor occurred. Furthermore, the questionnaire also collected data on sociodemographics (age, gender, educational level, marital status, profession), migration history (country of birth, country of birth of both parents, former place of residence in Egypt, total length of stay in Egypt, calendar year of migration to the Netherlands), vaccination against HBV infection, and any previous test results for HBV and HCV infection. Data regarding religious background were collected to be able to characterize the study population and assess whether the population would be representative for the population of Egypt. The religious background was assumed afterwards on the basis of the location of recruitment (i.e., those who were screened at mosques or weekend school were considered Islamic; those who were screened at the Coptic church were considered Christian. Those who were screened at the Public Health Service were asked to state their religion. A native Arabic medical student translated the Arabic answers on open questions from the questionnaires.

Clinical outcomes

At least one year after data collection, we evaluated whether or not participants with a chronic HBV or HCV infection were followed-up in care. With informed consent from these patients, clinical follow-up data were collected from the GP or hepatologist: the outcomes of ultrasound, fibroscan and/or liver biopsy (if performed); and treatment eligibility, initiation, and outcomes. Outcomes of fibroscan and/or liver biopsy were reported using the METAVIR system for fibrosis assessment (F0: no fibrosis, F1: portal fibrosis without septa, F2: few septa, F3: numerous septa without cirrhosis, F4: cirrhosis) [25].

In addition, participants were asked to complete a short questionnaire that evaluated prevention measures that resulted from diagnosis: reduction/cessation of alcohol intake; and knowledge of transmission routes and precautionary measures against further transmission.

Statistical analyses

Descriptive analyses were used to describe the characteristics of the participants. Prevalence of anti-HBc, HBsAg, anti-HCV and HCV RNA and corresponding 95% confidence intervals (CI) were calculated. Participants with indeterminate HCV antibody test results (EIA and RIBA indeterminate) who were HCV RNA negative were considered HCV antibody-negative. CI around prevalence were calculated via the Wilson method, using the binom package in the R statistical computing environment [26;27]. Using logistic regression analyses, we examined determinants of testing anti-HCV positive. Variables evaluated included socio-demographic variables, and the previously mentioned risk factors. Former place of residence in Egypt was categorized in geographic regions following Frank et al [9]. The region of longest residence was chosen if a participant had lived in more than one region. Variables with a p-value of ≤0.10 in univariate analyses were considered for entry in the multivariable logistic regression model. A stepwise backward selection procedure was used in the multivariable logistic regression model. A p-value of ≤0.05 was considered statistically significant. Odds ratios (OR) and CI in a table with one zero cell count were calculated via penalized logistic regression using the logistf package in R [27;28]. Otherwise, logistic regression in SPSS for Windows (SPSS version 17.0, SPSS Inc., Chicago) was used.

Results

Characteristics of participants

In total, 527 individuals were screened of which 465 were born in Egypt (see Figure 1). Those who were not born in Egypt (n=47; most were born in the Netherlands) and those for whom the country of birth was unknown (n=15) were excluded from the analyses. All of the 62 excluded individuals tested anti-HCV negative; six were anti-HBc positive, and all were HBsAg negative.

Of the 465 first-generation Egyptian migrants, median age was 43 years (IQR=36–49 years), and 57.4% (267/465) were male. The majority (58.3%, 271/465) was highly educated. Most participants were assumed Christian (69.2%, 322/465) and 30.8% (143/465) were assumed Muslim. The median year of migration to the Netherlands was 1995 (IQR=1988-2001); the median number of years in which participants had lived in Egypt was 25 (IQR=22-28 years). Most participants originated from Cairo (34.8%; 162/465); 12.7% (59/465) originated from Alexandria; 12.7% (59/465) from lower Egypt; 14.2% (66/465) from middle Egypt; 10.1% (47/465) from upper Egypt, and for 15.5% (72/465) the region of origin was unknown.

Prevalence of HCV and HBV infections

Prevalence of anti-HCV was 2.4% (11/465; 95%CI=1.3-4.2%). HCV RNA was detected in 2.2% (10/465; 95%CI=1.2-3.9%), of whom one individual was already aware of his chronic infection. Anti-HBc prevalence was 16.8% (78/465; 95%CI=13.7-20.4%). Five participants were chronic HBV carriers (HBsAg positive; 5/465; 1.1% [95%CI=0.5-2.5%]), of which two were already aware of their infection. No participants were co-infected with HBV and HCV. Because of the small numbers, no analyses were performed to identify determinants of testing HBsAg positive.

Determinants of HCV infection

In univariate analyses, older age, being widowed or divorced, anti-HBc-positive status, and exposure to PAT were significantly associated with being anti-HCV-positive (see table 1a). In multivariable analysis, older age and exposure to PAT remained significantly associated with HCV. Those who were exposed to PAT were at increased risk for HCV infection (OR=9.2, 95%CI=2.5-32.5) compared with those not exposed, and those who were born before 1960 were at increased risk for HCV infection (OR=4.6, 95%CI=1.1-26.7) compared with those born in 1970 or later, whereas the OR was 1.2 (95%CI=0.2-7.4) for those born between 1960 and 1969 (see table 1b).

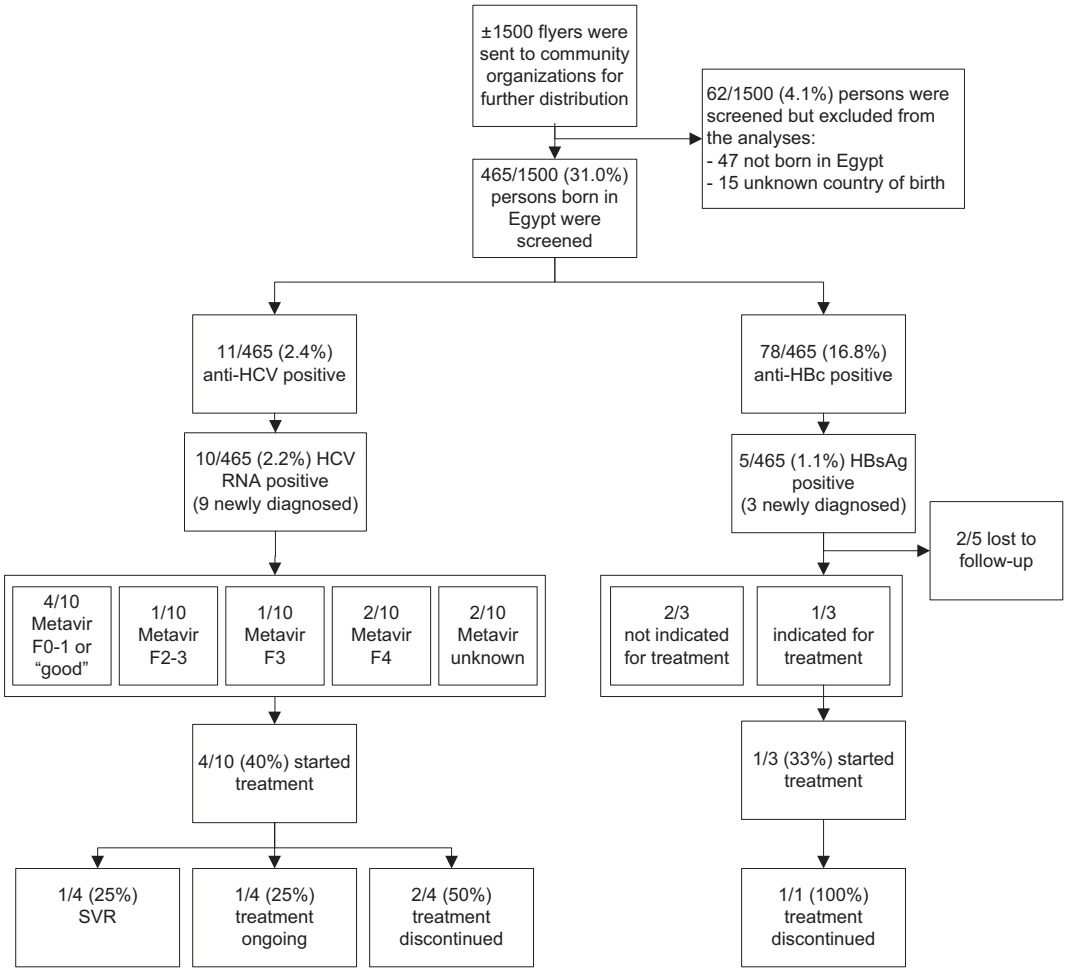

Figure 1. Overview of the recruitment procedures and clinical outcomes in a community-based screening programme for first-generation Egyptian migrants living in the region of Amsterdam in 2009-2010

Table 1a: Univariate logistic regression analyses of factors associated with testing hepatitis C virus (HCV) antibody positive among 465 Egyptian migrants participating in a community-based screening programme in the region of Amsterdam, the Netherlands, 2009-2010.

	HCV-antibody Negative (n=454) N	(%)	HCV-antibody Positive (n=11) N	(%)	Univariate OR (95% CI)
Socio-demographic variables					
Gender					
Male	259	(57.1)	8	(72.7)	1
Female	194	(42.7)	3	(27.3)	0.5 (0.1-1.9)
Unknown (missing)	1	(0.2)	0		
Education level					
Low	73	(16.1)	2	(18.2)	1
Medium	105	(23.1)	1	(9.1)	0.35 (0.0-3.9)
High	263	(57.9)	8	(72.7)	1.11 (0.2-5.3)
Unknown (missing)	13	(2.9)	0		
Calendar year of birth					
≥ 1970	199	(43.8)	2	(18.2)	1**
1960 - 1969	179	(39.4)		(27.3)	1.6 (0.3-9.4)
< 1960	74	(16.3)	6	(54.5)	7.0 (1.7-38.6)
Unknown	2	(0.4)	0		
Marital status					
Married or never married	425	(93.6)	8	(72.7)	1**
Widowed or divorced	28	(6.2)	3	(27.3)	5.7 (1.4-22.6)
Unknown (missing)	1	(0.2)	0		
Region of origin in Egypt					
Alexandria	57	(12.6)	2	(18.2)	1
Cairo	159	(35.0)	3	(27.3	0.5 (0.09-3.3)
Upper Egypt	46	(10.1)	1	(9.1)	0.6 (0.05-7.0)
Middle Egypt	65	(14.3)	1	(9.1)	0.4 (0.04-5.0)
Lower Egypt	56	(12.3)	3	(27.3)	1.5 (0.2-9.5)
Unknown (missing)	71	(15.6)	1	(9.1)	0.4 (0.04-4.5)
Living years in Egypt					
1-10 years	6	(1.3)	0		1
11-20 years	45	(9.9)	0		0.1 (0.0-27.5)
21-30 years	342	(75.3)	9	(81.8)	0.4 (0.0-48.3)
More than 30 years	53	(11.7)	2	(18.2)	0.6 (0.0-87.4)
Unknown (missing)	8	(1.8)	0		
Calendar year of arrival in the Netherlands					
Before 1989	110	(24.2)	5	(45.5)	1
1989-1995	118	(26.0)	3	(27.3)	0.6 (0.1-2.3)
1996-2001	112	(24.7)	3	(27.3)	0.6 (0.1-2.4)
2002 or later	104	(22.9)	0		0.1 (0.0-0.9)
Unknown (missing)	10	(2.2)	0		

Table 1a, *continued*	HCV-antibody Negative (n=454)		HCV-antibody Positive (n=11)		Univariate OR
Potential HCV risk factors	N	(%)	N	(%)	(95% CI)
Exposure to parenteral antischistosomal therapy (PAT)					
No / Don't know	419	(92.3)	6	(54.5)	1 **
Yes	27	(5.9)	5	(45.5)	12.9 (3.7-43.3)
Unknown (missing)	8	(1.8)	0		
AntiHBc status					
Negative	380	(83.7)	7	(63.6)	1*
Positive	74	(16.3)	4	(36.4)	2.9 (0.8-10.3)
Injecting drug use (IDU)					
No	421	(92.7)	11	(100)	1
Yes	1	(0.2)	0		12.2 (0.1-242.3)
Unknown (missing)	32	(7.0)	0		0.6 (0.0-4.5)
HCV infected mother					
No	443	(97.6)	11	(100)	1
Yes	11	(2.4)	0		1.7 (0.0-14.4)
HCV infection in social environment (not mother)					
No	326	(71.8)	6	(54.5)	1
Yes	128	(28.2)	5	(45.5)	2.1 (0.6-7.1)
Blood transfusion					
No / Yes, not in Egypt [a]	398	(87.7)	10	(90.9)	1
Yes, location Egypt	11	(2.4)	0		1.7 (0.0-14.3)
Yes, location unknown	13	(2.9)	1	(9.1)	4.2 (0.4-20.2)
Unknown (missing)	32	(7.0)	0		0.6 (0.0-4.7)
Hospital operation					
No / Yes, not in Egypt [a]	274	(60.4)	7	(63.6)	1
Yes, location Egypt	84	(18.5)	2	(18.2)	1.1 (0.2-4.1)
Yes, location unknown	63	(13.9)	2	(18.2)	1.4 (0.3-5.6)
Unknown (missing)	33	(7.3)	0		0.5 (0.0-4.7)
Medical injections					
No / Yes, not in Egypt [a]	172	(37.9)	3	(27.3)	1
Yes, location Egypt	109	(24.0)	3	(27.3)	1.6 (0.3-7.6)
Yes, location unknown	112	(24.7)	5	(45.5)	2.4 (0.6-10.6)
Unknown (missing)	61	(13.4)	0		0.4 (0.0-4.2)
Dentist					
No / Yes, not in Egypt [a]	239	(52.6)	4	(36.4)	1
Yes, location Egypt	84	(18.5)	5	(45.5)	3.5 (1.0-13.2)
Yes, location unknown	105	(23.1)	2	(18.2)	1.3 (0.2-5.8)
Unknown (missing)	26	(5.7)	0		1.0 (0.0-9.8)
Haemophilia treatment					
No	401	(88.3)	10	(90.9)	1
Yes, location Egypt	1	(0.2)	0		12.7 (0.1-254.2)
Yes, location unknown	3	(0.7)	0		5.5 (0.0-61.9)
Unknown (missing)	49	(10.8)	1	(9.1)	1.2 (0.1-5.1)

Table 1a, *continued* **Potential HCV risk factors**	**HCV-antibody Negative (n=454)** **N**	**(%)**	**HCV-antibody Positive (n=11)** **N**	**(%)**	**Univariate OR (95% CI)**
Haemodialysis					
No	420	(92.5)	11	(100)	1
Yes, location Egypt	0		0		
Yes, location unknown	1	(0.2)	0		12.2 (0.1-241.7)
Unknown (missing)	33	(7.3)	0		0.5 (0.0-4.4)
Hospitalization					
No / Yes, not in Egypt [a]	317	(69.8)	7	(63.6)	1
Yes, location Egypt	36	(7.9)	2	(18.2)	2.9 (0.5-11.4)
Yes, location unknown	63	(13.9)	2	(18.2)	1.7 (0.3-6.4)
Unknown (missing)	38	(8.4)	0		0.5 (0.0-4.7)
Circumcision					
No / Yes, not in Egypt [a]	121	(26.7)	3	(27.3)	1
Yes, location Egypt	141	(31.1)	5	(45.5)	1.3 (0.4-5.9)
Yes, location unknown	161	(35.5)	3	(27.3)	0.8 (0.2-3.6)
Unknown (missing)	31	(6.8)	0		0.6 (0.0-5.9)
Hijama					
No / Yes, not in Egypt [a]	392	(86.3)	11	(100)	1
Yes, location Egypt	5	(1.1)	0		3.1 (0.0-30.2)
Yes, location unknown	4	(0.9)	0		3.8 (0.0-39.0)
Unknown (missing)	53	(11.7)	0		0.3 (0.0-2.5)
Acupuncture					
No / Yes, not in Egypt [a]	401	(88.3)	10	(90.9)	1
Yes, location Egypt	3	(0.7)	0		5.5 (0.0-61.9)
Yes, location unknown	13	(2.9)	1	(9.1)	4.2 (0.4-20.3)
Unknown (missing)	37	(8.1)	0		0.5 (0.0-4.1)
Needle stick injury					
No / Yes, not in Egypt [a]	386	(85.0)	11	(100)	1
Yes, location Egypt	6	(1.3)	0		2.6 (0.0-24.2)
Yes, location unknown	18	(4.0)	0		0.9 (0.0-7.5)
Unknown (missing)	44	(9.7)	0		0.4 (0.0-3.0)
Drugs usage					
No	415	(91.4)	11	(100)	1
Yes, location Egypt	1	(0.2)	0		12.0 (0.1-238.8)
Yes, location unknown	7	(1.5)	0		2.4 (0.0-22.0)
Unknown (missing)	31	(6.8)	0		0.6 (0.0-4.6)
Tattoo					
No / Yes, not in Egypt [a]	284	(62.6)	9	(81.8)	1
Yes, location Egypt	59	(13.0)	0		0.3 (0.0-2.0)
Yes, location unknown	78	(17.2)	2	(18.2)	1.0 (0.2-3.5)
Unknown (missing)	33	(7.3)	0		0.4 (0.0-3.7)
Piercing					
No	385	(84.8)	11	(100)	1
Yes, location Egypt	3	(0.7)	0		4.8 (0.0-53.9)
Yes, location unknown	9	(2.0)	0		1.8 (0.0-15.5)
Unknown (missing)	57	(12.6)	0		0.3 (0.0-2.3)

Table 1a, *continued* Potential HCV risk factors	HCV-antibody Negative (n=454) N	(%)	HCV-antibody Positive (n=11) N	(%)	Univariate OR (95% CI)
Other blood contact					
No / Yes, not in Egypt [a]	376	(82.8)	11	(100)	1
Yes, location Egypt	2	(0.4)	0		6.5 (0.0-86.8)
Yes, location unknown	10	(2.2)	0		1.6 (0.0-13.5)
Unknown (missing)	66	(14.5)	0		0.2 (0.0-1.9)

Note. CI=confidence interval; *overall p-value ≤0.1 **overall p-value <0.05.
[a] Combined with the 'no'-category because only a small number of individuals experienced these risk factors outside of Egypt. Of those who did, most experienced them in high-income countries (mostly the Netherlands); one person had medical injections in Libya, one person had dental treatment in Kuwait, and one in Jordan.

Table 1b: Multivariable logistic regression analysis of factors associated with testing hepatitis C virus (HCV) antibody positive among 465 Egyptian migrants participating in a community-based screening programme in the region of Amsterdam, the Netherlands, 2009-2010.

	Multivariable Adjusted OR (95% CI)
Calendar year of birth	
≥ 1970	1**
1960 - 1969	1.2 (0.2-7.4)
< 1960	4.6 (1.1-26.7)
Exposure to parenteral antischistosomal therapy (PAT)	
No / Don't know	1**
Yes	9.2 (2.5-32.5)

Note. CI=confidence interval; **overall p-value <0.05

Genotyping and phylogenetic analyses

Sequences of the HCV-NS5B fragment were successfully obtained from all 10 HCV RNA-positive Egyptian migrants. All isolates were HCV genotype 4a. The obtained sequences, together with strains from other HCV genotype 4a -infected patients, were used for phylogenetic analysis. The analysis showed two epidemiological profiles. One profile consisted mainly of strains obtained from patients descending from Egypt and the Middle East; the other consisted of mainly Dutch IDU (the latter in bold; Figure 2). Although receiving little bootstrap support in this analysis, these two epidemiological profiles are considered to be distinct according to earlier detailed phylogenetic analysis, performed on combined NS5B fragments from HCV genotype 4-infected patients [20]. Sequences obtained from our study participants (n=10) all fitted within the first epidemiological profile, indicating that they are likely to have been infected with HCV in Egypt.

Amplification and sequencing of the S-region succeeded in all five HBsAg positive Egyptian migrants. All isolates were HBV genotype D. Phylogenetic analysis showed a high degree of phylogenetic clustering with HBV strains obtained from patients originating from the Middle East, and the analysis proved there was no link to other risk groups, like men who have sex with men and drug users (figure not shown).

Clinical outcomes

Seven out of ten HCV-infected participants gave informed consent for obtaining medical follow-up data; three self-reported data. Of those five who were infected with HBV, three gave informed consent, and two were lost to follow-up. Table 2 shows an overview of the clinical follow-up data for both HCV- and HBV-infected participants. In total, four of the ten HCV-infected participants started treatment; two discontinued, for one treatment is ongoing, and one successfully completed 12 months of treatment. However, follow-up was too short to determine sustained virologic response to treatment. For HBV infection, one of the three patients for whom data was available started treatment, but discontinued due to side effects.

Figure 2. Neighbor-joining tree based on the Tamura-Nei substitution model with γ-distribution (α=0.40). Phylogenetic analysis included HCV NS5B sequences of first-generation Egyptian migrants (n=10) identified in a community-based screening programme in Amsterdam in 2009-2010, and previously identified cases with genotype 4a HCV infection among various risk groups. Bootstrap values higher than 70 are shown (n=1000). Labels show the country of sampling, year of sampling, and GenBank accession number, or the study participation number (EG***). Black dots: study participants; open dots: previously diagnosed patients from Egypt; open squares: previously diagnosed patients from Iraq, Greece, Saudi-Arabia; black triangles: injecting drug users.

Table 2: Outcomes of clinical follow-up of 10 HCV- and 5 HBV chronically infected Egyptian migrants identified in a community-based screening programme in the region of Amsterdam, the Netherlands, 2009-2010.

Infection	Sex	Calendar year of birth	Aware of infection	Source clinical follow-up data	METAVIR score	Start treatment	Treatment outcome	Alcohol intake and knowledge on transmission routes [e]
HCV	F	1949	No	Clinician	F2 – F3	No [a]	N/A	Half (5/10) of the HCV-infected participants used alcohol prior to diagnosis. Three stopped alcohol use after diagnosis, and two limited their alcohol intake. The majority (7/10) were aware of transmission routes for HCV infection.
HCV	M	1953	No	Clinician	F4	Yes	Discontinued treatment at week 24 since virus was still detectable	
HCV	M	1954	No	Clinician	F4	Yes	Ongoing treatment	
HCV	M	1956	No	Clinician	F0 – F1	No [b]	N/A	
HCV	M	1958	No	Clinician	F0 – F1	No [a, b]	N/A	
HCV	M	1965	No	Clinician	Unknown	No [c]	N/A	
HCV	F	1972	No	Clinician	F0 – F1	No [b]	N/A	
HCV	M	1962	Yes [f]	Patient	Unknown	Yes	Successfully completed 12 months of therapy	
HCV	M	1964	No	Patient	F3	Yes	Discontinued treatment due to insufficient decrease in HCV viral load	
HCV	F	1978	No	Patient	"Good"	No [b]	N/A	
								Alcohol intake [e]
HBV	M	1962	No	Clinician	F0 – F1	No [d]	N/A	One of three participants used alcohol prior to diagnosis, and limited his alcohol intake after diagnosis.
HBV	M	1973	No	Clinician	N/A	Yes	Discontinued interferon treatment due to side effects	
HBV	F	1974	Yes [g]	Clinician	N/A	No [d]	N/A	
HBV	M	1959	No	N/A *	N/A	N/A	N/A	
HBV	F	1972	Yes [h]	N/A *	N/A	N/A	N/A	

Note. HCV = hepatitis C virus; HBV = hepatitis B virus; M = male; F = female; METAVIR F0 = no fibrosis, F1 = little fibrosis, F2 = medium fibrosis, F3 = severe fibrosis, F4=cirrhosis.

* Patients were lost to follow-up

[a] Contraindication for treatment; [b] Patients chose to defer treatment because of no or minimal fibrosis; [c] Reason unspecified; [d] No medical indication for treatment according to Dutch guidelines; [e] Data not available on individual patient level; [f] Patient tested positive in 2010, short before participation in this programme; [g] patient tested positive in 2000; [h] patient tested positive in 2003

Discussion

This community-based screening programme in the Netherlands demonstrated that screening of first-generation Egyptian migrants results in the identification of previously undetected HCV and HBV infections. Exposure to PAT and older age were strongly associated with anti-HCV-positive status. Furthermore, phylogenetic analyses showed that all HCV and HBV infections clustered with strains originating from Egypt and the Middle East, suggesting that infections were acquired in Egypt before migration to the Netherlands.

Although the anti-HCV and HBsAg prevalence among the Egyptian migrants (2.4% and 1.1%, respectively) is relatively high compared with the prevalence among the general Dutch population (0.3% [8] and 0.3-0.5%[29], respectively), it is much lower than the estimated prevalence in Egypt. This is in line with several studies in diverse migrant populations; lower prevalence than in the country of origin was found in a community-based screening programme for HCV and HBV infections among South Asian migrants in England [30], in a study among inhabitants of a multi-ethnic neighbourhood in the Netherlands [31], and in a prevalence study for HCV infection including migrants from Morocco, Surinam and Turkey in the Netherlands [32]. In a screening programme among first-generation Turkish migrants in the Netherlands, the HBsAg prevalence was in the lower range (3%) of the estimated prevalence in the general population in Turkey (2-8%) [33].

There are several potential explanations for the relatively low prevalence in comparison with the estimations from the country of origin. Migrants have a shorter exposure period to risk factors for viral hepatitis in the home country than those who remain. In our study, the median number of living years in Egypt was 25 years. In addition, migrants may represent a selected healthier group, often referred to as the 'healthy migrant hypothesis'. Although migration is dependent on multiple factors, this may also account for our study population, as almost half of them originated from regions of relatively low prevalence of HCV infection (Cairo and Alexandria) [9]. Another potential explanation has been described as the salmon bias hypothesis, according to which migrants who retire or suffer from disease are likely to return to their country of origin [34]. Finally, the study design may also have influenced the prevalence findings, since a community-based screening does not attract those who are already aware of their infection. On the other hand, people with increased exposure to risk factors for HCV or HBV infection, and those experiencing physical symptoms may be more likely to participate.

Given the relatively high educational level, the majority originating from Cairo and Alexandria, and the high proportion of Copts (69.2%), our study population is not representative of the general Egyptian population. The key question is whether our results can be generalized to the Egyptian migrant population. According to Egyptian migrant statistics, the Egyptian migrant population is highly educated; 77% who migrate to the United States and other OECD (Organisation for Economic Cooperation and Development) countries have tertiary education [35]. Furthermore, 37% of migrants from urban areas including Cairo and Alexandria moved to non-Arab countries compared with 10% or less for other Egyptian regions [36], possibly explaining the greater proportion of migrants from Cairo and Alexandria in our study. Limited data are available on the proportion of Copts among Egyptians that migrated, but one report suggests that Egyptian migrants to Australia are mostly Copts [37]. In addition, various websites (e.g., http://immigration-online.org/93-egyptian-immigration.html) suggest that Copts make up a large proportion of Egyptian migrants to non-Arab countries. Altogether, our study population may be well representative of Egyptian migrants living in non-Arab, high-income countries.

Our study showed that PAT exposure was strongly associated with anti-HCV-positive status, and those born before 1960 were at increased risk for HCV infection. The association between PAT and HCV infection has been described before [9]. The fact that older age was associated with HCV infection can be explained by the fact that these older people have had more lifetime exposure to risks for acquiring HCV infection. In addition, the hygienic standards of their childhood health care were likely lower compared with those born later, facilitating transmission of HCV infection. We did not identify any iatrogenic risk factors other than PAT to be significantly associated with anti-HCV positive status. However, six participants had antibodies to HCV but were not exposed to PAT. Recent publications suggest that iatrogenic transmission of HCV still occurs in Egypt [38;39]. In our study we found non-significant OR greater than 1 for some of the iatrogenic risk factors. The absence of statistically significant associations may be due to a lack of power.

Phylogenetic analysis suggests that the HBV infections that were identified in this study were acquired in Egypt. However, sexual transmission in the Netherlands from an Egypt-born partner is also a likely route for HBV transmission. We could not investigate this since data on sexual risk behaviour were not collected.

Community-based outreach screening can be an effective means of screening the Egyptian migrant population for HCV and HBV infection and for referral to care. We screened 14.5% (465/3,200) of first-generation Egyptian migrants aged 18 years or older living in the Amsterdam region, and we estimated the acceptance rate for screening at 31.0% (465/1500), assuming that each of the 1500 distributed flyers could result in one participant. These figures may be underestimated since some Egyptians may have been screened already because HCV infection is a well-known problem in Egypt. In comparison, other community-based screening programmes for HCV and/or HBV infection targeting migrants in the Netherlands have demonstrated screening rates varying from 13.0% [40] to 28.4% [41]. The majority of the identified Egyptian patients in our study visited a GP or hepatologist. The total costs for the screening programme were estimated at €49,500, including staff, laboratory costs, and recruitment costs. Related to the outcomes, it represents €106 (€49,500/465) per screened Egyptian, €3300 (€49,500/15) per person identified with a chronic HBV or HCV infection and €4125 (€49,500/12) per person newly identified with a chronic HBV of HCV infection. Treatment success was limited. For HCV, only one person successfully completed treatment within the study period. Previous cost-effectiveness analyses evaluating screening for HCV infection in populations with a similar prevalence and similar screening uptake rates as in our study were favourable [42;43]. However, Egyptians are predominantly infected with HCV genotype 4, which is a difficult to treat genotype. Therefore, a cost-effectiveness analysis of screening for HCV infection in the Egyptian population is needed to inform and underpin screening recommendations for this population. Such an analysis should include the scenario of simultaneous screening for HBV infection. Since the HBsAg prevalence in our population is relatively low (i.e., substantially lower [1.1%] than the lowest prevalence estimate that was used in a modelling study that showed that screening for HBV infection among migrants in the Netherlands is cost-effective [2.2%] [44]), screening for HBV infection only in first-generation Egyptian migrants may not be cost-effective compared with no screening. However, screening for HBV infection can be added at relatively low extra cost when screening for HCV infection is performed, and can result in identification of undetected chronic HBV infections, which in turn may lead to tracing of HBV-infected contacts, treatment if indicated, and prevention of further HBV transmission. In addition, since many people confuse HCV and HBV infections, a combined approach gives the opportunity to clarify transmission routes and prevention measures, and may increase the screening uptake.

In conclusion, the prevalence of HCV and HBV infections among Egyptian migrants in the region of Amsterdam is relatively low compared with the prevalence estimates in Egypt. However, first-generation Egyptian migrants are still at substantial higher risk for HCV and HBV infections compared with the general population in Western countries. Therefore, we suggest that all first-generation migrants from Egypt be considered for screening for HCV and HBV infections, especially those of older age and those exposed to PAT. Cost-effectiveness analyses are needed to inform future screening policies for this population. In addition, improvement in the treatment of chronic HCV genotype 4 infection is needed to prevent future morbidity and mortality related to HCV infection among Egyptians and other patients infected with this type.

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CHAPTER 5

GENERAL DISCUSSION

Hepatitis C virus (HCV) infection is a major public health problem with millions of individuals infected but yet to be diagnosed. Efforts in advancing therapeutic options for chronic HCV infection will only come to fruition when those infected are detected and able to access specialized health care. Low awareness for HCV infection among the general population and health care professionals is a huge problem for scaling up diagnosis and treatment of HCV-infected individuals. Increased awareness and effective screening strategies are needed to decrease future HCV-related morbidity and mortality.

The studies presented in this thesis focus on the feasibility and effectiveness of various HCV screening strategies to identify the population of HCV-infected individuals hidden among the general population. This population that, amongst others, is comprised of first-generation migrants, individuals who received a blood transfusion before 1992, and individuals who experimented with injection drugs in the remote past, has been estimated to account for 66% of the total HCV-infected population in the Netherlands [1]. We conducted a systematic review of the international literature (see chapter 2), and synthesized points for future consideration in new screening programs. An Internet-based HCV screening program, which incorporated findings from the systematic review, was developed, applied and evaluated (see chapter 3). The evaluation of that program resulted in the launch and evaluation of a different approach for the identification of undiagnosed HCV infections: A community-based screening program for HCV and hepatitis B virus (HBV) infection for first-generation migrants from Egypt (see chapter 4). This chapter summarizes the main results of the studies presented in this thesis, and their implications for future HCV screening programs, policy and further research in the Netherlands.

5.1 Hepatitis C screening programs worldwide

A systematic review was performed to synthesize the literature on screening programs for HCV infection and distil effective characteristics and strategies for the identification of HCV-infected individuals hidden among the general population (see chapter 2). We identified 67 screening programs for HCV infection in 15 countries. Of these, 41 programs were integrated within already existing health care facilities, 24 programs were not integrated and exclusively set up for screening, and two programs used both strategies. The programs identified a total of ~25,500 HCV-infected individuals: only a small proportion of the estimated total HCV-infected population (i.e., 130-170 million people [2]). Most programs were carried out in low prevalence countries for HCV infection, such as the Netherlands. Comparison of the programs was hindered by the lack of reported data on program characteristics and clinical outcomes, and the heterogeneity in organization and screening procedures. Moreover, only few programs used a comparison group to assess effectiveness. Therefore, no firm conclusions could be made as to which program characteristics or strategies (e.g., free versus low-cost screening, anonymous versus non-anonymous screening, opt-in versus opt-out screening, use of particular media to promote screening) are most effective in attracting or motivating individuals for screening, or in attracting those at higher risk for HCV infection. However, some patterns in the data were observed. In general, low prevalence rates of HCV infection were found in programs targeting health care workers, in antenatal clinics programs, and in programs conducted in sexually transmitted diseases (STD) and general practitioner (GP) clinics in which no pre-screening risk selection was used. In general, high prevalence rates of HCV infection were observed in programs that used a pre-screening selection based on risk factors for HCV infection (especially a history of injecting drug use, elevated alanine aminotransferase [ALT] or migrant status), in programs that

were carried out in high prevalence countries or regions for HCV infection, and in programs in psychiatric clinics.

It was striking that only one study reported the use of motivational communication based on psychosocial theory to promote the screening program. Health promotion programs that are theory-based are more likely to be effective than those that are not [3]. In addition, none of the screening programs reported the use of simple but effective tools to increase test uptake, such as reminder messages or goal setting tools [e.g., 4]. Another surprising finding was that none of the programs, not even those of recent years, reported the use of Internet as a medium to promote the screening and inform individuals about HCV infection. The Internet offers the opportunity to provide information that is tailored to the individuals' needs and reaches and interacts with a large audience beyond the setting of health care facilities. Moreover, its anonymous character may prove particularly suitable for providing information and screening for a stigmatized disease such as HCV infection.

Implications for hepatitis C screening programs

The review clearly indicates that more effective, large-scale screening programs are needed to decrease the HCV-related burden of disease in an era of potent therapy for chronic HCV infection. With respect to the development of screening programs for HCV, results from the systematic review suggest that in low prevalence populations the use of pre-screening selection criteria should be considered to increase efficiency. Program characteristics and outcomes, including start of treatment, should be reported systematically to improve comparability of programs. In addition, programs should use comparison groups, or ideally conduct randomized trials to be able to better assess effectiveness, and improve future programs. We also suggest that screening programs should be based on psychosocial theory, and incorporate tools such as reminder messages to increase testing uptake. Finally, we propose that the Internet may be a useful medium for promotion and facilitation of HCV screening.

5.2 Internet-based screening for hepatitis C

The first HCV screening program in the Netherlands commenced in 2007. At that time, epidemiological data on prevalence of HCV infection in various risk groups in the Netherlands were yet to be collected. For most individuals in the general Dutch population, HCV infection was a rather unknown disease, associated with a career in drug use, and often confused with hepatitis A virus or HBV infections for which vaccines are available. Data on socio-cognitive determinants of HCV testing were lacking. However, treatment options for chronic HCV infection had improved significantly. Therefore, it was considered that there was no time to wait for these data or postpone the development of HCV screening programs. To identify undiagnosed HCV-infected individuals, a pilot Internet-based screening program was initiated. The program aimed to evaluate whether HCV screening of risk groups hidden among the general population would be feasible and effective through a public media campaign in combination with a low-threshold blood testing procedure (see chapter 3). The screening program applied most of the suggestions for screening that resulted from the systematic review of HCV screening programs. The screening program included a pre-screening risk selection tool, psychosocial theory-based communication for its promotion, Internet as a delivery tool to ensure a low-threshold and anonymous character, and tools to stimulate the uptake of testing. The following section describes how these features were incorporated into the program.

Organization of the Internet-based screening program

On the basis of prevalence studies that were previously published, risk factors for HCV infection were determined and a questionnaire was developed that assessed risk for HCV infection (see 3.1). The questionnaire was evaluated among a population of liver patients with known HCV status prior to its online use in the screening program. Sensitivity was relatively high and specificity somewhat lower; although sensitivity and specificity were low compared with levels applicable to blood screening tests, they were considered to be fairly good for a questionnaire relying on the memory (and reporting) of potential risk factors for HCV infection, with the purpose of functioning as a pre-screening selection tool. The positive predictive value depends on the prevalence in the population using the questionnaire [5]. The higher the prevalence in the population filling out the questionnaire, the better its predictive value. Therefore, the promotional campaign of the screening program was designed to especially motivate participation of risk groups for HCV infection.

Since data on socio-cognitive determinants of HCV testing were lacking, the campaign was based on concepts from the revised health belief model [6]. It aimed to increase perceived susceptibility among those at risk for HCV infection by addressing potential risk factors for acquiring HCV infection. In addition, perceived severity of HCV infection, and benefits of screening through the program were communicated to the public. Since the screening program served as a pilot in the urban region of Amsterdam and the sub-urban region of South Limburg, only regional media could be used to attract participants. Because of budgetary constraints, we were limited in the number of radio, television and newspaper advertisements and banners that could be employed. Free publicity for the screening program was sought through press releases and support from a PR specialist.

The campaign referred individuals to the risk assessment questionnaire at the project's Website. The Website and questionnaire were available in Dutch, English, Spanish, French, Turkish and Arabic to facilitate participation for migrants who did not have sufficient knowledge of the Dutch language. Translation of the Website was time consuming and a technical challenge due to the many foreign characters and the right alignment of the Arab language.

After participation in the risk assessment questionnaire, those at risk for HCV infection were motivated to get a blood test via a low threshold testing procedure. The Website provided a referral letter to a testing laboratory, along with instructions and addresses of the participating laboratories. Each referral letter carried a unique identification code. Participants could print, download, or send the referral letter to an email address. They could also opt to receive an email and/or short message service (SMS) reminder message, which was sent 5 days later. In addition to the reminder service, the project included a virtual appointment planner as a tool to increase testing uptake. The screening program design included extensive data gathering mechanisms and access to all screening and test results, in order to document each step related to coverage; the number of unique individuals recruited to screening and testing; the proportion identified as "at risk"; the proportion that tested positive for anti-HCV antibodies; and the number treated.

Feasibility and effectiveness of the Internet-based screening program

Although the volume of the program was lower than anticipated, we found that risk- and Internet-based screening for HCV infection was feasible and effective. Over 95% of those who started the risk assessment questionnaire completed it. Of those who completed the questionnaire and were advised to seek HCV testing via the Internet-based testing procedure, 28% complied and opted for testing. We believe this is substantial considering the large step between filling out an online questionnaire

and visiting a laboratory for a blood draw. An HCV screening program in Hungary that also used an Internet-based approach, including a risk assessment questionnaire and referral of those who reported risk for HCV infection to the GP for testing, did not measure compliance with the advice to seek testing, which limited a testing uptake comparison with that program [7]. Since we are not aware of any other Internet-based screening programs for HCV, we used a similar STD-screening program for comparison. An Internet-based screening program for syphilis that was targeted at men who have sex with men [8] had a much lower testing uptake (10%) compared with our program.

Among those who were tested, prevalence of anti-HCV antibodies was 3.6% (95% CI=2.1%-5.7%), which is more than 16 times the estimated prevalence in the general Dutch population (0.22%) (see 3.2). This indicates that the risk assessment questionnaire succeeded in selecting a population at higher risk of HCV infection. Using the prevalence among those who tested via the project, the pre-test probability of disease, i.e., the prevalence of HCV infection among those who completed the risk assessment questionnaire was estimated at approximately 1.5% using Fagan's nomogram (see 3.1, page 77). This indicates that the theory-based media campaign did especially motivate those at higher risk for HCV infection, and not the 'worried well', to visit the Website and complete the questionnaire. The Internet-based procedure for confirmation testing was successful. Communicating preliminary test results for HCV infection anonymously via the Internet, followed by a face-to-face consultation for confirmation testing and referral, did not lead to infected individuals being lost to follow up. All individuals who were found with chronic HCV infection belonged to the hidden population of HCV-infected individuals, and would probably not have been identified without the public media screening program. They were referred to follow-up care, and half of them started treatment.

Usability and acceptability of the screening procedure as perceived by participants was high (data not presented in this thesis). Usability and acceptability were measured following methods by Davis [9]. All individuals who completed the risk assessment questionnaire were asked to participate in the usability and acceptability study, and 22.2% (2146/9653) agreed to participate. They filled out an online questionnaire measuring perceived ease-of-use of completing the online risk assessment questionnaire (Cronbach's α=.81, n=4), and the usefulness (Cronbach's α=.89, n=5) and acceptability (Cronbach's α=.87, n=4) of the online risk assessment. Scores on all three measures were very high (4.8 [SD=0.4], 4.4 [SD=0.7], and 4.6 [SD=0.6] on five-point Likert scales [1=low; 5=high], respectively), indicating that Internet-based screening is easy to use, useful, and an acceptable method for risk assessment for HCV infection. Although promising, there may be some limitations to this study. First, one might expect that individuals who agreed to participate in such a program have a more positive attitude towards it compared with those who did not participate. However, the participants did not have any experience with the service beforehand, and could also have been disappointed. Furthermore, there may be selection bias as this sub-study was done in a self-selected sample of participants in which women, those of older age, and those with medium-to-high educational level were overrepresented.

Potential improvements to the Internet-based screening program

Although we conclude that risk- and Internet-based screening for HCV infection is feasible and acceptable, there are some potential effectiveness improvements that could be made. The first relates to the volume of the project's reach. The screening program attracted over 40 thousand individuals within a 21-month period. Almost 10 thousand individuals completed the risk assessment questionnaire, only 5300 of these were from the pilot regions Amsterdam and South Limburg, and

of these, 1480 individuals were at risk for HCV infection. Although the Website was available in six languages, non-Western migrants were underrepresented among participants, and only 1.1% of those who completed the questionnaire used the Website in a language other than Dutch.

The limited volume of the project's reach is attributed to the restricted reach of the regional media campaigns that were used in the project. Towards the end of the project, a 1-day national media event was arranged, and an immediate peak in exposure and testing was observed (data not shown in this thesis). Besides the higher number of individuals who are exposed to national media compared with regional media, national media also tend to create a snowball effect in information dissemination: Once a topic gains national media exposure in the Netherlands, it is often observed that various media, both national and regional, will also cover the topic (e.g., various television and radio stations, newspapers and news websites). In a similar, but national, screening program for HCV infection in Hungary (population size: 9.96 million [10]), nearly 200 thousand individuals completed an online risk assessment questionnaire during a two-year campaign [7]. Although the two programs are not completely comparable due to differences in media budget, media effectiveness and cultural differences, we recommend that national media be used to achieve the maximal exposure needed to reach hidden populations at risk for HCV infection in the future. To reach non-Western migrants, we suggest conducting community-based activities in addition to national media and Internet-based programs, since uptake through the Internet may not be sufficient, and migrants can also be targeted at specific venues such as churches and mosques. Such an approach is only feasible for relatively large migrant groups.

Another potential improvement to the Internet screening program for HCV infection relates to user acceptance and attrition. A relatively small proportion (39%) of the initial visitors to the screening program Website started the risk assessment questionnaire. It is unknown whether those who dropped out were at risk for HCV infection or not. In addition, although we were pleased with the uptake of blood-testing of 28%, a further increase in testing uptake (and thus decrease in attrition) could improve the effectiveness of screening programs. We identified several variables that were independently associated with compliance with advice to test for HCV. Individuals of older age, higher educational levels, with residence in a less urbanized region, and those without health insurance were more likely to be tested. Those who reported non-injecting drug use were less likely to be tested compared with other risk groups for HCV infection. Two more practical variables were found: those who received a reminder message and those who lived closer to the laboratory that carried out the testing were more likely to be tested than those who did not receive a reminder message and those who lived further away from the laboratory, respectively. Hence, we suggest that screening programs should use reminder messages and facilitate testing close to the community of interest.

However, for improvement of future screening programs, we wished to gain more in-depth understanding of why some people who receive online advice to test for HCV infection comply with that advice while others do not, and the role of the online testing procedures in compliance and noncompliance with testing advice. Therefore, we studied the reasons for compliance or noncompliance with advice to test for HCV infection through the service by means of qualitative research (see 3.3). We found that features specific to the online testing procedure, such as the autonomous nature of the testing procedure and the personalized testing advice, played a significant role in motivation to test for HCV infection. However, some features were considered problematic. For example, the lack of obligatory procedures for testing, and the lenient deadline for testing (which

was set at a calendar year) led to a lack of commitment among participants and were identified as reasons for not getting tested. Also, some participants had problems printing the laboratory form. For improvement of future Internet-based screening programs, we suggest that commitment with the program should be established by providing individuals with a clearly defined and relatively tight deadline for testing. Technical printing problems could be overcome by offering to send the laboratory form by post or by having the forms emailed to mobile phones or to the laboratories directly. To further lower traveling and/or printing barriers, future screening programs may consider the use of home collection tests or at-home tests (self tests) for HCV, once reliable tests become available for consumer use. A recently developed oral fluid-based rapid test for HCV, which is currently licensed for professional use only, could become a promising tool for future screening programs [11;12].

In addition to the practical reasons for noncompliance related to the Internet-based testing procedure, low perceived vulnerability, low perceived severity, discouraging individuals in the social environment, the avoidance of threatening information, and fear for the consequences of a positive test result were reported reasons for not testing for HCV infection. Although quantitative research is needed to study the association between the reported reasons and testing, it suggests that both procedure-related and psychological factors need to be addressed to increase testing uptake. Although most psychosocial determinants were addressed within the screening program's information, several strategies can be used to increase effectiveness of communication. For example, low perceived vulnerability was based on downplaying of personal risk. The program's Website did address personal risk, but apparently not convincingly enough for all participants. Scenario-based risk information that addresses doubts about personal risks and the consequences of downplaying risk can be an effective strategy to improve the understanding and perception of personal risk.

Slow diffusion, low acceptance, and attrition are major challenges for Web-based services. Although the low-threshold nature of the Internet offers many advantages, its nonobligatory character makes it difficult to keep users and create commitment. The use of participatory design methods, i.e., incorporating the proposed end user's perspective into the design of the intervention (that is, user-centered design), can lead to eHealth interventions better customized to individual preferences and user profiles, and therefore may positively influence the uptake of Web-based services [13]. User-centered design strategies are, for example, the development of user profiles or persona [14], and prototyping [15]. If a user-centered design had been used in the Internet-based screening program for HCV infection, several of the reported barriers for screening may have been prevented. As a result we recommend the use of the ceHRes roadmap for the development of future Web-based services: a holistic framework for the development of sustainable eHealth technologies that incorporates user-centered design and business modeling [16]. The business modeling component of that roadmap focuses on the development of a service that is sustainable, by identifying and addressing the needs of important stakeholders with respect to the service [17]. The development of sustainable screening programs (i.e., programs that become institutionalized) is another important issue that requires attention, especially in screening programs that are not integrated within existing health care facilities. This is expanded upon in 5.5.

5.3 Community-based hepatitis B and C screening for first-generation migrants

Migrants are considered to account for the majority of HCV infections in many high-income countries including the Netherlands. However, migrants were underrepresented among the participants of our Internet-based screening program, despite the fact that the risk assessment questionnaire was multilingual and migrant-specific media were used to promote the program. We hypothesized that a community-based screening program would be an efficient strategy for attracting large migrant groups for screening and identifying undiagnosed infections. Therefore, we organized a community-based screening program targeting first-generation migrants from Egypt who were living in the Amsterdam region (see chapter 4). The prevalence of HCV infection in this group was estimated to be substantial, since Egypt is the country with the world's highest prevalence (estimated at 15%) due to the use of unsterilized injection material in large-scale parenteral antischistosomiasis therapy campaigns from the 1920s to 1980s [18;19]. As a result of an expressed desire from the Egyptian community for simultaneous screening for both HCV and HBV infection, and considering Egypt is a medium endemic country for HBV infection, risk factors for HCV and HBV infection are overlapping, and HCV and HBV infection often are confused, we decided to offer screening for both HCV and HBV infection.

Feasibility and effectiveness of the community-based screening program

The outreach community-based screening program turned out to be feasible. During 11 educational and screening sessions, a total of 465 first-generation migrants from Egypt were screened. They represent a substantial proportion (14.5%) of the target population. The prevalence of anti-HCV antibodies and HBsAg were 2.4% (95% CI=1.3-4.2%) and 1.1% (95% CI=0.5-2.5%), respectively, considerably higher than the infection prevalence that is observed in the general Dutch population, but lower than the estimated prevalence in the country of origin. This is in line with several studies in diverse migrant populations [20-22], and suggests that in general, migrants comprise a group at lower risk of infection compared with those who remain. Possible explanations are the shorter exposure period to risk factors in the home country, the healthy migrant hypothesis (a selected healthier group opts for migration), and the salmon bias hypothesis (migrants who retire or suffer from disease are likely to return to their country of origin [23]). Alternatively, the prevalence in the home country may be overestimated. The study design may also have influenced the prevalence findings, since a community-based screening does attract a selected population (i.e., those who are already diagnosed are less likely to participate, whereas those who experience symptoms may be more likely to participate). Most of the identified infections were newly diagnosed. Exposure to parenteral antischistosomal therapy and older age were strongly associated with positive anti-HCV status, and phylogenetic analyses suggested that infections were acquired in the region of origin before migration to the Netherlands.

Community-based screening may lower travel- or time-related barriers for screening, but those who are identified with an infection still need to visit medical care facilities for follow-up care. This kind of follow up in regular care settings after diagnosis through community-based screening may be challenging. However, the majority of the individuals who were diagnosed through our program visited a GP or hepatologist. Perhaps the low threshold consultation with a visiting hepatologist for those with chronic HCV infection which was arranged at the Public Health Service facilities motivated individuals to attend and visit the hospital thereafter. Although the follow up to medical care was successful, the treatment outcomes were somewhat disappointing. All individuals were

infected with HCV genotype 4, which is relatively difficult to treat with the standard therapy options. New therapies currently being developed may improve the future treatment benefits for Egyptians and others infected with this genotype. Despite the fact that treatment success was limited, the detection of HBV or HCV infection may still be beneficial. First, patients can limit their alcohol intake to reduce liver damage, take precautionary measures to prevent transmission to others, and, for HBV infection, susceptible contacts can be protected by vaccination. In addition, detection of viral hepatitis can offer an explanation for long standing health complaints. In our screening program, we found that some of the patients who were identified with chronic HCV infection had unexplained physical complaints (e.g., fatigue and malaise) for which they had seen specialist doctors at the hospital. Surprisingly, they were not tested for HCV infection at that time, although Egypt is well-known for its HCV epidemic. It suggests that health care professionals should be more aware of risk groups for HCV infection, and should suggest screening sooner for those who were born in intermediate to high prevalence countries. The psychological effects for those who are diagnosed but untreated are unknown, but they can be both positive and negative; it could be beneficial when diagnosis gives an explanation for long-term physical complaints, while it could prove detrimental for otherwise healthy individuals.

Challenges and practical lessons learned from the community-based screening program

Although the program was considered feasible, the efficient use of resources in the community-based screening program was challenging. The screening strategy remains labor-intensive and therefore relatively expensive and the number of individuals who will present themselves for screening is hard to estimate. Sometimes only few people attended, while on other occasions people had to wait in line for hours to be screened. The screening sessions at the Coptic church had the highest attendance, probably because of the large number of people that attended the church services prior to the screening sessions. We observed that the Coptic church serves not only as a location for practicing religion, but also as a social meeting place where community members meet each other on a weekly basis. Reaching the Islamic community was more difficult, as the leaders of the local mosque only agreed to one screening session for men and women, respectively. The sessions were organized in between two religious services, and some individuals who were in line for the screening left when the next service started. The other organizations (e.g., an organization for Egyptian women) had far less members compared with the church and mosque, and, although the educational sessions were very interactive, the number of individuals who were screened was limited.

Drawing blood from individuals in the Egyptian population was time-consuming. Despite the fact that the nurses were very experienced at drawing blood from individuals with veins that are difficult to locate (i.e., injecting drug users), many Egyptians (mostly women) had thin and deep veins. The use of non-invasive screening methods (e.g., using oral fluid or dried blood spot tests) may shorten the on-site screening procedure per person. However, they have the disadvantage that individuals cannot be given a definite test result and have to return for confirmation blood testing. A community-based HCV and HBV screening program in the United Kingdom found that a substantial proportion of patients with reactive oral fluid test results during community-based screening declined to access support for their infection, despite home visits of health care professionals to persuade individuals to attend the hospital, and a free taxi service to and from the local hospital [20].

5.4 Other hepatitis C screening programs for risk groups among the general Dutch population

This paragraph reflects on HCV screening programs in the Netherlands that were not included in the systematic review (see chapter 2) because they were not published, or published after July 2010 (the review includes papers published between 1991 and July 2010).

National hepatitis C campaign
Following two pilot studies in 2008 [24;25], a national hepatitis C information campaign was launched in the Netherlands in 2009 [26;27]. The campaign aimed to increase awareness for HCV infection among the general population and health care professionals, and aimed to increase risk perception, information seeking behavior and testing among risk groups for HCV infection. The campaign consisted of two interventions; a public intervention targeting the general population, specific risk groups for HCV infection within the general population (among which first-generation migrants), GPs, and Public Health Services; and an intervention targeting hard drug users in addiction care. The public intervention was implemented in the six largest cities in the Netherlands. Information about HCV infection, risk groups and treatment options were disseminated through mass media, brochures and posters at GP clinics, social services and pharmacies, and through community-based informative meetings. A website provided additional information about diagnostics and prognosis of HCV infection, and offered the online risk assessment questionnaire that is described in 3.1 of this thesis. Those at risk for HCV infection were referred to their GP to discuss testing. At the same time, GP practice staff was systematically trained by regional GP support organizations, through group meetings and individual education. They also received educational material on HCV infection. Public Health Services' staff was trained on how to organize community-based informative meetings for migrant groups and received educational material for these groups. The community-based screening program, described in chapter 4, was initially one of these initiatives for migrants, but was extended into a program in which both education and screening were offered. The public intervention lasted for 6 months. The hard drug users intervention was implemented nationally. Hard drug users attending addiction care were actively approached and were offered individual consultations, group educational sessions, and HCV testing. Addiction care professionals were provided with educational materials. This intervention lasted for 18 months.

The outcomes of the national campaign were modest. Based on annual reports of 25 laboratories in the Netherlands, an estimated 1554 additional HCV tests and 49 positive anti-HCV antibody tests were attributed to the public intervention [26]. In the drug users intervention, a total of 1130 HCV tests and 299 positive anti-HCV antibody tests were registered. All were attributed to the intervention because it was considered that HCV testing in drug addiction care was scarce beforehand. However, the effect of the intervention may have been somewhat overestimated since in some regions (e.g., Amsterdam) routine HCV testing of hard drug users in addiction care did already take place before the intervention [28]. Although the drug users intervention was considered cost-effective, the cost-effectiveness of the public intervention was modest [26]. The somewhat disappointing result of the national campaign could be partially explained by the H1N1 influenza virus pandemic that happened to occur at that time. The pandemic created a heavy workload for GPs and Public Health Services, and captured virtually all the attention of the media, professionals and the public. This demonstrates the vulnerability of a largely GP-based screening program. Another explanation for the modest result was the relatively short duration of the campaign for gaining access to migrant groups and

organizing informative sessions [27]. The time-consuming nature of community-based programs has been discussed earlier in this chapter.

Screening programs for migrant groups

Several ad-hoc screening programs for HCV infection targeting migrant groups in the Netherlands have been performed. Programs aimed at first-generation Turkish migrants in Arnhem [29], first- and second-generation Chinese migrants in Utrecht [30] and Amsterdam [31], and first-generation Egyptian migrants in Amsterdam (see chapter 4) used a community-based approach. The programs screened 13.0%, 28.4%, 18.4%, and 14.5% of the respective target populations, and found anti-HCV antibody prevalence rates of 0.4% (95% CI=0.0-1.3%), 0.4% (95% CI=0.0-1.3%), 0.2% (95% CI=0.0-0.9%), and 2.4% (95% CI=1.3-4.2%), respectively. To note, the programs targeting migrants from Turkey and China were primarily designed to identify HBV infections, but also included HCV in their screening offer.

Another screening program in Arnhem selected first-generation migrants from Vietnam, Afghanistan, Iraq, Iran, and former Soviet Union countries from the municipal administration and invited them for HBV and HCV screening at the Public Health Service [32]. The total screening uptake was 26.9% (927/3447). Although the screening uptake among migrants from former Soviet Union countries was the lowest (10.9%), the prevalence of chronic HCV infection in this group was the highest (3.1%; 95% CI=0.4-10.7, 2/65). The screening uptake in the other groups was relatively high (26.3%-36.5%), whereas prevalence of HCV infection was low (varying from 0% [95% CI=0.0-2.4%] to 0.5% [95% CI=0.0-2.9%]). As with most programs that were mentioned in the preceding paragraph, this project was primarily designed to identify HBV infections but included HCV in the screening offer.

From these screening programs for migrant groups, we can conclude that the total number of identified HCV infections is low. Although estimations indicate that migrants account for most HCV infections in the Netherlands, most of the migrant groups that were reached so far do probably not account for these infections. Other explanations may be that a selected sub-group at lower risk for HCV infection participated, or, although unlikely, that a substantial proportion of the HCV-infected migrant population is already diagnosed. Alternatively, the estimation that migrants from HCV endemic countries account for most HCV infections in the Netherlands may be incorrect. The parameters for the prevalence of HCV infection in this group that were used in that study (0.4% [min] to 1.6% [max]) are based on relatively small sample sizes. Especially the maximum prevalence estimate (1.6%) has a relatively wide 95% confidence interval (0.4% to 2.9%). In addition, prevalence estimates for HCV infection of the countries of origin were used to determine which migrants groups are at a high risk for HCV infection (i.e., migrants from countries with an estimated prevalence of anti-HCV antibodies of $\geq$ 2%). Since for many countries these estimates are uncertain, the size of the high-risk migrant population in the Netherlands may have been overestimated.

5.5 Future directions for hepatitis C screening in the Netherlands

The studies in this thesis show that the strategies that have been used so far are limited in their effectiveness in diagnosing HCV-infected individuals. Moreover, effectiveness of screening programs refers to successfully improving long-term health outcomes. The reported outcomes of most screening programs are usually the number of detected infections and do not include the clinical outcomes that may result from screening. Furthermore, data from randomized controlled trials that follow screened and unscreened populations through to morbidity and mortality are not available. Therefore, HCV screening has only been considered to be effective because many HCV-infected persons are presumed to be undetected, treatment for chronic HCV infection has shown to be beneficial, and the HCV-related morbidity and mortality in the absence of screening interventions have been estimated to increase [33].

There is no one screening strategy that seems most effective in diagnosing HCV-infected individuals hidden among the general population, and all strategies have their limitations. In addition, the local context (e.g., risk group distribution, background prevalence, health care facilities) influences the potential effectiveness of a strategy. Therefore, a joint venture between local public health entities and GPs and other already existing clinics using a variety of strategies may be the best approach. The following paragraphs discuss various screening strategies for HCV infection.

Screening at GP clinics

Integrated screening at the GP clinic seems the most logical way to offer screening because of its integration within community health care. There are several strategies for HCV screening at the clinic. First, through opportunistic screening in which the GP proposes HCV screening of patients potentially at risk for HCV infection during their consultation for something that is unrelated to HCV infection. However, studies in the United States and the United Kingdom have shown that knowledge about HCV infection among GPs is suboptimal [34-36]. In a Dutch study, only half of the HCV-infected patients in primary care were referred to secondary care, even after publication of the Practice Guideline for GPs [37]. A lack of knowledge regarding risk factors and improved treatment options for HCV infection for which referral is warranted, limits the effectiveness of case finding for HCV infection at the GP clinic. A study in the Netherlands showed that the addition of a practice support intervention leads to improvements in medical consciousness regarding HCV infection, which in turn may lead to better case finding [24]. Medical consciousness regarding HCV infection can also be improved by offering refresher courses for GPs.

Besides opportunistic screening, an automated screening alert for all individuals who are found with an ALT elevation at the GP clinic may be promising. A study in the Netherlands estimated the prevalence of chronic HCV infection among those with ALT between 50-100 IU/L at 1.4% (95% CI=0.7-2.9%), and put forward that through using this strategy in the Netherlands an estimated 1200 to 1300 HCV-infected patients could be identified at the GP clinic on an annual basis [38]. A study from the USA showed that HCV screening of those with ALT >40 IU/L would identify 50% of those infected with HCV [39]. The Dutch scenario is based on follow-up testing of those screened for ALT as a part of regular care. The scenario from the USA, however, is unrealistic as it is based on a theoretical scenario in which all individuals are screened for ALT. On the other hand it does show that when all individuals with elevated ALT would be screened, at least half of all HCV infections will remain undetected. Therefore, additional screening strategies are needed.

Screening at the GP clinic can also be organized by inviting all patients by mail to complete a risk assessment questionnaire, and subsequently offer screening to those who report a risk factor for HCV infection. The risk assessment questionnaire can be offered both offline and online, limiting the workload related to the processing of paper-and-pencil questionnaires. Such a questionnaire could include risk factors for all kinds of diseases, for example other infectious diseases (e.g., HBV and HIV infection), diabetes, cardiovascular diseases, cancer, etc.
Although integrated screening via GP clinics is promising, there are some difficulties. As mentioned previously, once individuals are diagnosed with chronic HCV infection at the GP clinic, they should be referred to the hospital for further diagnostics and treatment if indicated. Although the current level of knowledge and the referral rate among GPs in the Netherlands are unknown, previous publications suggest that these may be suboptimal. This may limit the effectiveness of screening at the GP clinic. In addition, the current political movement in the Netherlands towards vertical substitution of care (the transfer of tasks from specialist to GP) for the management of chronic diseases may decrease the capacity of GPs for case finding of HCV infection. Furthermore, although the laboratory costs for screening at the GP clinic are covered by health insurance, as of January 2013, people in the Netherlands will have to pay the first 350 euro of medical costs themselves. Hence, for otherwise healthy individuals, screening for viral hepatitis can be expensive and may pose a financial burden on families. In light of this the above mentioned screening strategies could be considered unethical in a situation where awareness about personal risk is raised in individuals or families who cannot afford the screening costs.

Screening at other clinics

The systematic review (see chapter 2) indicated that screening visitors of psychiatric clinics could detect a substantial number of HCV infections. However, since psychiatric disorders may pose a contraindication for treatment of chronic HCV infection, screening of patients in such a clinic should be discussed thoroughly with treatment specialists, perhaps on an individual patient level. Furthermore, screening in STD or antenatal clinics can be useful, but only if risk factors for HCV infection (e.g., [former] injecting drug use or HIV infection) are present. A recent study showed a favourable cost-effectiveness for adding HCV screening to the already existing screening program for all pregnant women (currently including HBV, HIV and syphilis), but only in the best-case scenario. In the base-case analysis, cost effectiveness was considered moderate when only first-generation migrant women from non-western countries were offered screening [40].

A potential effective screening strategy that has not yet been investigated in the Netherlands is the screening of legal migrants from HBV- or HCV-endemic countries upon entry to the Netherlands. Such a screening could be integrated within the already existing screening for tuberculosis in which migrants, foreign students and foreign workers from high-prevalence countries for tuberculosis who intend to stay at least 3 months are referred to the Public Health Service for screening by the immigration office [41]. The uptake of tuberculosis screening is high (>80% within 3 months of arrival), since it is a prerequisite for obtaining a residence permit. We suggest performing a pilot study that examines the feasibility of this screening approach.

Population-based screening

In the USA, the cost-effectiveness of a one-time screening intervention of the adult population in addition to the current approach of risk-based screening was investigated. It was concluded that, when considering a participation rate of 15%, the intervention would likely be cost-effective relative

to current practice [42]. A sub-analysis showed that screening of only high-risk birth cohorts could be even more cost effective if implementation costs, pace of adoption by clinicians, and median age of diagnosis were similar. As a result, the US Centers for Disease Control and Prevention recently recommended one-time HCV screening of persons born between 1945 and 1965 who are living in the USA [33]. It was estimated that baby boomers account for 81.6% of all anti-HCV antibody positive persons [39]. The prevalence of anti-HCV antibodies in baby boomers was estimated at 3.25%, considerably higher than the estimated prevalence among adults aged 20 years or older who were born outside of the birth cohort (0.8%).

Although one-time birth cohort screening seems well worth examining, there are some drawbacks. First, the uptake of screening is essential to its effectiveness. Although a relatively low uptake of 15% was assumed in the cost-effectiveness model in the USA, those who participate may not be representative for the total population of baby boomers. It may be that those at lower risk for HCV infection (i.e., the worried-well) could be more likely to respond. From the population-based screening administration for cervical cancer in the Netherlands, it is known that those who respond more often are at lower risk than those who do not respond, and those with lower socioeconomic status and migrants are less likely to participate [43]. Thus, although it may be promising, the effectiveness of such an intervention needs to be demonstrated in practice.

In the Netherlands, the estimated prevalence of HCV infection in the general population is much lower compared with the USA, and the majority of infections are estimated to occur in first-generation migrants. Therefore, a one-time screening intervention of the general population or a specific birth cohort seems less obvious, and research is needed to examine its potential effectiveness. However, when considered appropriate, it may be offered in conjunction with the population-based screening for bowel cancer which will commence its first screening invitations in 2013. In that program, men and women between the ages of 55 and 75 years will be offered a home kit to collect a stool sample every two years. In 2019, following its preparatory stage, the program will invite all four million persons in that age group who are living in the Netherlands, thus including all persons born between 1944 and 1964. It may pose an opportunity for a one-time HCV screening of baby boomers in the Netherlands. Since the bowel screening program will use home-collection tests, in such a scenario the use of a similar test for HCV should also be considered. The effectiveness of this strategy, however, is related to the uptake of bowel cancer screening, which needs to be evaluated after implementation.

Screening outside the clinic

Although integration of HCV screening at the GP clinic and/or other already existing health care facilities seems most logical, those who do not visit these facilities will not be reached unless extra efforts are undertaken to attract individuals to these facilities (e.g., via personal invitations). The studies in this thesis have shown that screening beyond the clinic can be feasible. Internet-based screening seems useful for identifying HCV infections among former injecting drug users, whereas community-based screening seems useful for identifying infections among migrants.

However, none of the Dutch programs described in this thesis and in 5.4 compared different screening strategies. Therefore, in line with the findings from the systematic review (see chapter 2) the assessment of effectiveness of various screening strategies is problematic. To our best knowledge there is only one study, from the United Kingdom, that compared three screening strategies for migrants at risk for HCV and HBV infection [44]. In this study, a community awareness campaign

was organized and five thousand testing cards were distributed to mosques. The cards contained an integrated virology form, and encouraged individuals to visit their GP for viral hepatitis testing. Secondly, a GP clinic offered all Pakistani/British Pakistani patients screening (opportunistic approach). Thirdly, another clinic evaluated an opt-out approach where all target patients were contacted by letter inviting them to opt out of screening. Those who did not opt out were telephoned and asked to attend screening clinics. The opt-out strategy proved the most effective; 20% of those who were contacted were screened, which was 1.4% and 0% for the opportunistic and community strategies, respectively.

Although we believe that screening outside the clinic is useful since in-clinic screening is usually limited to those who attend the clinic and dependent on awareness and capacity in primary health care, there are some limitations and challenges that need to be addressed. First, as mentioned previously, the effectiveness of such programs depends largely on both the self-referral of individuals for screening which leads to a selection in participation, and the participation rate. Screening programs outside the clinic have to attract their participants and, in the absence of financial resources for campaigning, have to invest in contacts with community organizations and press agencies for free publicity. Moreover, gaining media attention for HCV screening programs that are scattered throughout the year is difficult.

Second, such programs often lack institutionalization and are relatively expensive when compared to screening in already existing health care facilities. Hence, when resources become scarce, they are likely to end and thus are not a long-term option for screening. In addition, there is no reimbursement system for programs that offer anonymous screening, such as Internet-based screening programs. Although the Internet is a relatively low-cost medium for organizing screening outside the clinic, the costs associated with Internet-based screening comprise not only laboratory costs and costs for health professionals who are involved, but also costs for website development, maintenance and promotion.

Another disadvantage of screening programs that are aimed at the public but not part of a national screening policy is their heterogeneity: they often target different populations (e.g., Chinese migrants, Egyptian migrants, Turkish migrants), and are inconsistent in their screening offer (e.g., some include both HCV and HBV screening whereas others screen for HCV or HBV infection only; some offer free vaccination against HBV infection whereas others do not). This does not contribute to a common awareness among the general population about risk groups for HCV and HBV infection, and also causes inequality and confusion since individuals with risk factor X living in region A will receive free screening and/or HBV vaccination, whereas individuals with risk factor X living in region B will not.

National screening policy

In recent years, many screening programs for HCV (and/or HBV) infection have been performed in the Netherlands, and epidemiological data have been collected. It is time to synthesize the knowledge and experiences, identify and address the existing gaps in knowledge, and formulate and implement a national screening strategy that specifies the groups that should be targeted for screening as well as the most appropriate screening strategies and their prerequisites for effectiveness. Such a plan should also consider the capacity of specialist care to ensure that patients, once identified, can receive adequate care. In several high-income countries, national plans to address the HCV and HBV burden of disease have been developed [e.g., 45-48]. These plans can serve as a background for Dutch screening policy, but need to be adapted to the epidemic and context in the Netherlands.

In order to determine which groups best to target for screening, first, insight into the undiagnosed population of HCV- (and HBV-)infected individuals is needed. This can be achieved by mapping the size of the HCV-infected population and the diagnosed population per risk group. In the current Dutch situation, however, it will be difficult to gain insight into the size and characteristics of the diagnosed population. First, for chronic HCV infection there is no surveillance system since only acute HCV infections have to be notified; chronic HCV infection is not a notifiable disease. Second, there is no national database in which chronically infected patients' characteristics and treatment data are registered. Such a database does exist for HIV [49], and has proven its value. A database of similar design should be set up for HCV (and HBV) infection. We also suggest changing the notification policy for HCV infection since notification of all HCV RNA positive-individuals would benefit the surveillance of HCV infection.

Future screening in the general population

Given the current knowledge and experiences, we suggest that screening at GPs should be intensified by implementing an automated screening alert for HCV screening for patients with elevated ALT, and by inviting GP patients at higher risk for infection for screening via an opt-out testing procedure. The latter might be accompanied by practice support and education for GP clinic staff. In addition, Internet-based and community-based screening programs beyond the GP clinic should be organized to lower testing barriers and give individuals the opportunity to opt for screening without discussing risk factors with the GP. Such programs should be organized and promoted nationally during a limited period once a year to benefit from the reach of national media. They should use theory and knowledge regarding determinants facilitating participation in screening programs in their communication, and incorporate tools to increase test uptake (e.g., reminder messages). All community-based screening programs should be consistent with respect to risk factors and risk groups for HCV (and HBV) infection, and include a follow-up trajectory for those identified with chronic infection. All screening activities should be incorporated into a national screening policy for viral hepatitis and systematically evaluated, and adapted if needed. Public Health Services should play an important role in the organization of Internet-based and community-based screening programs. Screening of high-risk patients in clinical care (e.g., drug users, HIV-infected individuals) should be continued and intensified.

Cost-effectiveness analyses comparing different screening strategies (e.g., GP-based screening only; GP-based and community-based screening; GP-based, community-based and internet-based screening) should be performed. In addition, the cost-effectiveness of combined HCV and HBV screening in migrant groups compared with screening for one infection only should be determined. In migrant populations with relatively high prevalence of HCV infection, but relatively low prevalence of HBsAg as is the case for Egyptian migrants, merely screening for HBV infection may not be cost-effective, and vice versa. However, screening for HBV and HCV can be combined at relatively low extra cost and can result in identification of undetected infections. For HBV, it may lead to tracing of HBV-infected contacts, treatment if indicated, and prevention of further HBV transmission by vaccination of negative contacts. Moreover, a combined approach provides the opportunity for clarification of transmission routes and prevention measures, and may increase screening uptake. We therefore suggest screening for HCV and HBV infections in first-generation migrants from HBV and/or HCV endemic countries simultaneously.

5.6 Limitations and implications for future research

There are several limitations in the studies described in this thesis. First, the systematic review only included screening programs that were published. Not all screening programs are necessarily published, and programs that were successful in the identification of infected individuals may be more likely to be published than unsuccessful programs. Therefore, the outcomes of the review may not be representative of all HCV screening programs worldwide. Second, the Internet-based and community-based screening programs that are presented in this thesis did not include a comparison group, and therefore cannot assess the effectiveness of their screening strategy for the identification of undiagnosed individuals. Also, we did not perform cost-effectiveness analyses to evaluate the economic feasibility of both strategies. The qualitative study into reasons for compliance and noncompliance with advice to test for HCV infection (see 3.3) was helpful to understand testing behavior. However, quantitative research should be performed to assess the association between HCV screening and the determinants that were identified to inform future screening campaigns.

For future research, studies are needed to estimate the undiagnosed HCV-infected population per risk group. We also suggest studying the cost-effectiveness of combined screening for HCV and HBV infection in migrants, as well as cost-effectiveness of Internet-based and community-based screening in addition to GP-based screening, and screening of new entrants in tuberculosis clinics. To limit the uncertainty of such analyses through the use of parameters from literature, screening programs should routinely collect data regarding the proportion of newly identified individuals, the proportion of individuals that require treatment, treatment uptake and outcomes, and for HBV, the results of contact tracing.

5.7 Concluding remarks

The studies presented in this thesis showed that Internet-based and community-based screening strategies are feasible and could prove useful in screening for other diseases. The internet-based screening program attracted high risk groups for HCV infection, and demonstrated a high blood testing uptake. The identified HCV-infected individuals belonged to risk groups that are hidden among the general population. However, investments are needed to increase the reach of such programs. This thesis and other studies showed that thus far HCV screening programs have only identified a small proportion of the estimated number of HCV infections. It illustrates that no one screening strategy can reach all target populations and that different screening strategies and large-scale programs are necessary.

On the basis of this thesis' studies and discussion, we present the following recommendations:

- Screening programs should systematically report program characteristics and outcomes including clinical follow-up, and preferably include comparison groups to assess effectiveness of their screening strategies.
- Internet-based screening programs should include multiple tools and strategies to increase testing uptake, such as reminder messages, a clearly defined relatively tight deadline for blood testing, proximate testing locations, and solutions to technical problems. In addition, psychosocial determinants of HCV testing should be addressed using persuasive theory-based communication strategies.
- Screening programs should use national media and extensive campaigns to maximize their reach.

- Community-based screening programs for first-generation migrants from endemic countries should offer screening for HCV and HBV infection simultaneously.
- Non-invasive HBV and HCV tests should be considered for community-based and internet-based screening programs. At-home tests may become a promising tool for future screening programs.
- Future research should gain insight into the undiagnosed population per risk group, and compare the cost-effectiveness of different screening strategies.
- Ad-hoc HCV screening programs for migrants should be halted. The current knowledge about screening program effectiveness should be synthesized, resulting in a uniform national action plan in which several screening strategies are combined.

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APPENDICES

SUMMARY
SAMENVATTING
DANKWOORD
BIOGRAFIE

SUMMARY

Hepatitis C virus (HCV) infection is a major worldwide public health problem with millions of individuals infected but yet to be diagnosed. Over time undiagnosed chronic HCV infections may lead to liver cirrhosis, liver cancer, and death. Since antiviral therapeutic options for chronic HCV infection have improved substantially over recent years and are likely to improve further in the near future, effective screening strategies are needed to identify undiagnosed HCV infections. This thesis focuses on innovative approaches for the identification and screening of HCV-infected individuals hidden among the general population. This population that, among others, is comprised of individuals who experimented with injection drugs in the remote past, individuals who received a blood product transfusion before 1992, and first-generation migrants, has been estimated to account for 66% of the total HCV-infected population in the Netherlands. This thesis examines the feasibility and effectiveness of HCV screening strategies targeting this population.

Hepatitis C screening programs worldwide

Chapter 2 describes the results of a systematic review of the international literature concerning HCV screening programs designed to reach the hidden population of HCV-infected individuals. We aimed to identify screening program characteristics and strategies that were effective in identifying undiagnosed infections. We found that the published programs identified only a small proportion of the estimated HCV-infected population. They were very heterogenic in their organization and screening procedures. Comparison of the programs was hindered by a lack of reported data on program characteristics and clinical outcomes, such as the initiation of treatment after diagnosis. Most programs did not include a control or comparison group to assess effectiveness. In general, high prevalence rates of HCV infection were observed in programs that used a pre-screening selection based on risk factors for HCV infection (in particular a history of injecting drug use, elevated alanine aminotransferase, or migrant status), in programs that were carried out in countries or regions with high prevalence of HCV infection, and in programs in psychiatric clinics. In general, low prevalence rates of HCV infection were found in programs targeting health care workers, in antenatal clinic programs, and in programs conducted in sexually transmitted diseases and general practitioner clinics in which no pre-screening risk selection was used. The reported use of motivational communication based on theory and/or determinants facilitating screening, and tools to increase HCV screening uptake were virtually absent.

We suggest that in low prevalence populations pre-screening selection criteria should be considered to increase efficiency. In addition, to be able to assess screening program effectiveness, there is a need for programs using a comparison group. To improve comparability of future screening programs and outcomes, we propose parameters for the reporting of screening programs worldwide. Finally, we suggest that screening programs should incorporate theory-based motivation-increasing components in order to increase screening uptake.

Internet-based screening for hepatitis C infection

The third chapter of this thesis describes the development and evaluation of an Internet-based HCV screening program in the Netherlands. As was proposed through the systematic review, a pre-screening risk selection was used to identify those at risk for HCV infection. In 3.1 the development of a risk assessment questionnaire for HCV infection is described. The sensitivity and specificity of the risk assessment questionnaire were evaluated in a sample of liver patients with known HCV status, yielding sensitivity and specificity of 84.6% and 63.8% respectively.

A Web-based, multilingual version of the questionnaire was used for the Internet-based screening program (see 3.2). In that program, a theory-based public media campaign was set up in the regions of Amsterdam and South Limburg to increase awareness and stimulate HCV testing among risk groups. The campaign communicated risk factors for HCV infection and referred individuals to the online risk assessment questionnaire. Those who were determined to be at risk through the questionnaire were advised to seek blood testing for HCV. An Internet-based, low-threshold, anonymous blood testing procedure was organized through the project's Website. Reminder messages and a virtual appointment planner were incorporated to increase testing uptake. Blood test results could be obtained via the Internet using a personal identification code. Those with reactive test results were referred to the Public Health Service for confirmation testing, and referral to a hepatologist was arranged for those chronically infected with HCV. Clinical follow-up data were collected >12 months after the screening program.

Over one quarter of the individuals who completed the questionnaire reported a risk factor for HCV infection and were advised to seek blood testing. Reporting a risk factor for HCV infection was independently associated with female gender, a low or unknown educational level, older age, being born outside of the Netherlands, and not having health insurance. The uptake of blood testing was substantial. Seeking HCV testing was independently associated with older age, a medium or high educational level, living in South Limburg compared to living in Amsterdam, living closer to a laboratory, not having health insurance, receiving a reminder for testing, and risk group for HCV infection (those who reported non-injecting drug use were less likely to take the test compared with other risk groups). The prevalence of HCV infection among participants was considerably higher than the estimated prevalence in the general Dutch population. Most of those with chronic HCV infection reported former injecting drug users, and about half started treatment. Although the project was feasible and effective in the identification of HCV-infected individuals in the general population, the reach of the regional media campaigns was limited, and migrants were underrepresented among the project's participants.

In 3.3 a qualitative study of reasons for compliance and noncompliance with advice to seek blood testing through the Internet-based screening program is described. Features specific to the online testing procedure played a significant role in motivation to test for HCV infection. For example, the fact that the testing procedure allowed individuals access to a test without having to discuss or explain their desire to be tested with their general practitioner, motivated individuals to take the test. However, some features were considered problematic. For example, the lenient deadline for testing caused low commitment to the service, which was a reason for noncompliance. In addition to reasons for compliance and noncompliance related to the Internet-guided testing procedure, we identified reasons unrelated to the online testing procedure. For example, perceived benefits of testing and high perceived vulnerability were reported reasons for testing for HCV infection, whereas low perceived vulnerability and fear for the consequences of a positive test result were reported reasons for not testing for HCV infection.

Community-based screening for hepatitis B and C infection

As migrants were underrepresented in the Internet-based screening program, we sought an alternative approach to reach that population. Therefore, we organized and evaluated a community-based screening program for HCV and hepatitis B virus (HBV) for first generation migrants from Egypt living in the Amsterdam region (see chapter 4). Since Egypt is the country with the world's highest prevalence of HCV infection, we hypothesized that a substantial number of undiagnosed

HCV-infected individuals could be identified through the screening of Egyptian migrants. The program also included screening for HBV infection because of its overlapping risk factors with HCV infection, and the fact that treatment options for HBV infection have improved in recent years. Egyptian migrants were recruited for educational and screening sessions at various Egyptian organizations (e.g., mosques, churches). Data regarding demographics and risk factors for HCV infection were collected using a standardized questionnaire. Chronically infected patients received referrals and follow up. Clinical follow-up data were collected from clinicians >12 months after the screening program. Phylogenetic analyses were used to ascertain the geographic origin of infections. The program reached a substantial proportion of the Egyptian migrant population for screening. Prevalence of HCV and HBV infection were higher compared with the estimated prevalence in the general Dutch population, but lower compared with the estimated prevalence in the general Egyptian population. HCV infection was independently associated with exposure to parenteral antischistosomal therapy and older age. Strains of those chronically infected with HCV and HBV were typical of those of Egypt and the Middle East, suggesting that infection occurred in the region of origin before migration. About half of those diagnosed with chronic HCV infection started treatment.

Concluding remarks

The studies presented in this thesis showed that Internet-based and community-based screening strategies are feasible and could prove useful in screening for other diseases. The internet-based screening program attracted high risk groups for HCV infection, and demonstrated a high blood testing uptake. The identified HCV-infected individuals belonged to risk groups that are hidden among the general population. However, investments are needed to increase the reach of such programs. This thesis and other studies showed that thus far HCV screening programs have only identified a small proportion of the estimated number of HCV infections. It illustrates that no one screening strategy can reach all target populations and that different screening strategies and large-scale programs are necessary.

On the basis of this thesis' studies and discussion, we present the following recommendations:

- Screening programs should systematically report program characteristics and outcomes including clinical follow-up, and preferably include comparison groups to assess effectiveness of their screening strategies.
- Internet-based screening programs should include multiple tools and strategies to increase testing uptake, such as reminder messages, a clearly defined relatively tight deadline for blood testing, proximate testing locations, and solutions to technical problems. In addition, psychosocial determinants of HCV testing should be addressed using persuasive theory-based communication strategies.
- Screening programs should use national media and extensive campaigns to maximize their reach.
- Community-based screening programs for first-generation migrants from endemic countries should offer screening for HCV and HBV infection simultaneously.
- Non-invasive HBV and HCV tests should be considered for community-based and internet-based screening programs. At-home tests may become a promising tool for future screening programs.
- Future research should gain insight into the undiagnosed population per risk group, and compare the cost-effectiveness of different screening strategies.
- Ad-hoc HCV screening programs for migrants should be halted. The current knowledge about screening program effectiveness should be synthesized, resulting in a uniform national action plan in which several screening strategies are combined.

SAMENVATTING

Hepatitis C virus (HCV) infectie is een belangrijk probleem voor de volksgezondheid met wereldwijd miljoenen mensen die besmet zijn, maar nog niet gediagnosticeerd. Ongediagnosticeerde chronische HCV-infecties kunnen op den duur leiden tot levercirrose, leverkanker en de dood. Aangezien antivirale therapeutische middelen voor chronische hepatitis C infectie onlangs aanzienlijk zijn verbeterd en de komende jaren waarschijnlijk nog beter zullen worden, zijn effectieve strategieën voor screening nodig om ongediagnosticeerde HCV-infecties op te sporen. Dit proefschrift richt zich op innovatieve strategieën voor het opsporen en screenen van HCV-geïnfecteerde personen die verborgen zijn in de algemene bevolking. Deze populatie, onder andere bestaande uit mensen die in het verleden experimenteerden met injecterend druggebruik, mensen die een bloedtransfusie kregen vóór 1992 en eerste generatie migranten, vormt naar schatting 66% van de totale HCV-geïnfecteerde populatie in Nederland. De haalbaarheid en effectiviteit van screeningstrategieën voor hepatitis C gericht op deze populatie werden onderzocht.

Screeningprogramma's voor hepatitis C wereldwijd

Hoofdstuk 2 beschrijft de resultaten van een systematische review van de internationale literatuur naar hepatitis C screeningprogramma's gericht op het opsporen van de verborgen populatie van HCV-geïnfecteerde personen. Het doel van deze studie was het vinden van kenmerken en strategieën van screeningprogramma's die mensen met niet-gediagnosticeerde HCV infecties op een effectieve manier identificeerden. We vonden dat de gepubliceerde programma's slechts een klein deel van de totale geschatte HCV-geïnfecteerde populatie identificeerden. De programma's waren erg verschillend in hun organisatie en screeningprocedures. Door het ontbreken van gerapporteerde gegevens met betrekking tot programmakenmerken en klinische uitkomsten, zoals het starten van behandeling, konden de programma's slecht met elkaar vergeleken worden. De meeste programma's gebruikten geen controle- of vergelijkingsgroep om hun effectiviteit te kunnen vaststellen. In het algemeen werden hoge prevalentiecijfers gevonden in programma's die een pre-screening selectie op basis van risicofactoren voor HCV infectie hanteerden (in het bijzonder ooit-injecterend druggebruik, verhoogde alanine aminotransferase, en het behoren tot een migrantengroep), in programma's die werden uitgevoerd in landen of regio's met een hoge prevalentie van HCV infectie en in programma's in psychiatrische klinieken. In het algemeen werden lage prevalentiecijfers gevonden in programma's gericht op personeel in de gezondheidszorg, in programma's in klinieken voor zwangere vrouwen en in programma's in soa-polikliniek of huisartspraktijken waar geen pre-screening risicoselectie werd gebruikt. Er werd vrijwel niet gerapporteerd over het gebruik van motiverende communicatie op basis van sociaal psychologische theorieën of over hulpmiddelen voor het vergroten van de participatie aan de programma's, zoals herinneringsberichten. Onze aanbeveling voor landen met een lage prevalentie van HCV infectie is om pre-screening selectiecriteria te gebruiken om de efficiëntie van screeningprogramma's voor HCV infectie te vergroten. Om de effectiviteit van screeningprogramma's te kunnen bepalen, zijn programma's nodig die een controle- of vergelijkingsgroep gebruiken. Daarnaast zouden screeningprogramma's vaste parameters moeten rapporteren om toekomstige programma's en hun uitkomsten te kunnen vergelijken en evalueren. Tot slot zouden screeningprogramma's zich moeten baseren op theorie en hulpmiddelen moeten gebruiken om de participatie aan de programma's te vergroten.

Screening voor hepatitis C met behulp van het internet

Het derde hoofdstuk van dit proefschrift beschrijft de ontwikkeling en evaluatie van een internet-screeningprogramma voor HCV infectie in Nederland. Zoals uit de systematische review naar voren kwam, werd een pre-screening risicoselectie gebruikt om mensen met risico op HCV infectie te identificeren. In 3.1 wordt de ontwikkeling van dit instrument, namelijk een risicovragenlijst voor

HCV infectie, beschreven. De sensitiviteit en specificiteit van de risicovragenlijst werden geëvalueerd in een populatie leverpatiënten met een bekende HCV status. De sensitiviteit en specificiteit waren respectievelijk 84,6% en 63,8%. Een online versie van deze vragenlijst werd vervolgens meertalig aangeboden in het internet-screeningprogramma (zie 3.2). In dat programma werd een op sociaal-psychologische theorieën gebaseerde publieke mediacampagne opgezet in de regio's Amsterdam en Zuid-Limburg om het bewustzijn voor HCV infectie te vergroten en risicogroepen te stimuleren zich te laten testen. De campagne communiceerde risicofactoren voor HCV infectie en verwees mensen naar de online risicovragenlijst. Mensen die volgens de vragenlijst risico hadden gelopen op HCV infectie werden geadviseerd om een HCV bloedtest te laten doen. Zij konden zich met behulp van het internet op een laagdrempelige manier anoniem laten testen. Herinneringsberichten en een virtuele afspraakplanner werden in het programma opgenomen om het testgedrag te bevorderen. De bloedtestresultaten konden via het internet worden opgevraagd met behulp van een persoonlijke identificatiecode. Degenen met positieve testresultaten (antilichamen) werden doorverwezen naar de GGD voor een bevestigingstest en mensen met een chronische HCV infectie werden verwezen naar een hepatoloog. Klinische follow-up gegevens werden >12 maanden na de screening verzameld.

Ruim een kwart van de mensen die de vragenlijst invulden rapporteerde een risicofactor voor HCV en werd geadviseerd om een bloedtest te laten doen. Het rapporteren van een risicofactor was onafhankelijk geassocieerd met vrouwelijk geslacht, laag of onbekend opleidingsniveau, hogere leeftijd, geboren zijn buiten Nederland en het niet hebben van een ziektekostenverzekering. De proportie mensen die een bloedtest liet doen was aanzienlijk. Het doen van een HCV bloedtest was onafhankelijk geassocieerd met een hogere leeftijd, een gemiddeld of hoog opleidingsniveau, het woonachtig zijn in Zuid-Limburg in vergelijking met Amsterdam, het dichter bij een laboratorium wonen, het niet verzekerd zijn voor ziektekosten, het ontvangen van een herinnering voor het testen, en de risicogroep voor HCV infectie (mensen die niet-injecterend drugsgebruik rapporteerden waren minder geneigd om zich te laten testen in vergelijking met andere risicogroepen). De hepatitis C prevalentie onder de deelnemers was aanzienlijk hoger dan de geschatte prevalentie onder de algemene Nederlandse bevolking. De meeste mensen met chronische HCV infectie rapporteerden ooit-injecterend druggebruik en ongeveer de helft startte met behandeling. Hoewel het project haalbaar en effectief was voor de identificatie van HCV-geïnfecteerde personen in de algemene bevolking, was het bereik van de regionale mediacampagnes beperkt en waren migranten ondervertegenwoordigd onder de deelnemers van het project.

In 3.3 wordt een kwalitatieve studie beschreven naar de redenen voor het al dan niet opvolgen van het advies voor een bloedtest in het internet-screeningprogramma. Specifieke kenmerken van de online testprocedure speelden een belangrijke rol in de motivatie om te testen op HCV infectie. Zo vormde het feit dat mensen een test konden doen zonder hun risico of motivatie met hun huisarts te bespreken een reden voor mensen om zich te laten testen. Echter, sommige elementen waren problematisch. Zo zorgde het ontbreken van een strakke deadline voor het doen van de bloedtest voor een lage betrokkenheid bij de service. Dat was een reden voor het niet opvolgen van het testadvies. We vonden ook redenen voor het al dan niet opvolgen van het testadvies die niet waren gerelateerd aan de testprocedure. Zo werden de voordelen van testen en een hoge perceptie van kwetsbaarheid aangemerkt als redenen voor testen, terwijl lage waargenomen kwetsbaarheid en angst voor de consequenties van een positief testresultaat genoemd werden als redenen voor het niet testen op HCV infectie.

Screening op hepatitis B en C op locatie

Omdat migranten ondervertegenwoordigd waren in het internet-screeningprogramma werd naar een andere strategie gezocht om deze groep te bereiken. Hierop werd een (community-based) screening op locatie voor HCV en hepatitis B virus (HBV) infectie georganiseerd. Het programma was bedoeld voor eerste generatie migranten uit Egypte die woonachtig waren in de regio Amsterdam (hoofdstuk 4). Aangezien Egypte het land is met ‘s werelds hoogste prevalentie van HCV infectie, veronderstelden we dat we met de screening van Egyptische migranten een groot aantal ongediagnosticeerde HCV-geïnfecteerde personen konden identificeren. Het screeningprogramma omvatte ook screening op HBV infectie vanwege de overlap in risicofactoren met HCV infectie en het feit dat de behandelingsmogelijkheden voor chronische HBV infectie in de afgelopen jaren verbeterd zijn. Egyptische migranten werden via verschillende Egyptische organisaties (bijvoorbeeld moskeeën en kerken) benaderd voor voorlichting- en screeningsessies. Gegevens met betrekking tot demografie en risicofactoren voor HCV infectie werden verzameld met behulp van een gestandaardiseerde vragenlijst. Chronisch geïnfecteerde deelnemers werden verwezen naar het ziekenhuis en opgevolgd. Klinische follow-up gegevens werden >12 maanden na de screening verzameld. Fylogenetische analyses werden gebruikt om de geografische herkomst van de gevonden infecties vast te stellen. Het programma heeft een aanzienlijk deel van de Egyptische migrantenbevolking bereikt en gescreend. De prevalentie van HCV en HBV infectie was hoger in vergelijking tot de geschatte prevalentie onder de algemene Nederlandse bevolking, maar lager in vergelijking tot de geschatte prevalentie onder de algemene Egyptische bevolking. HCV infectie was onafhankelijk geassocieerd met blootstelling aan injecties tegen schistosomiasis en hogere leeftijd. De virusstammen van de mensen met een chronische HCV of HBV infectie waren kenmerkend voor die uit Egypte en het Midden-Oosten, wat suggereert dat de infecties hebben plaatsgevonden in de regio van herkomst, voor migratie. Ongeveer de helft van de mensen met chronische HCV infectie startte met behandeling.

Conclusies

De studies in dit proefschrift laten zien dat screeningstrategieën voor HCV infectie via internet en op locatie haalbaar zijn en mogelijk ook nuttig voor screening op andere ziekten. Het internet-screeningprogramma slaagde erin om hoogrisicogroepen voor HCV infectie aan te trekken en een groot deel van de mensen met risico liet zich testen. De personen die gevonden werden met een HCV-infectie bleken tot risicogroepen te behoren die verborgen zijn in de algemene bevolking. Echter, investeringen zijn nodig om het bereik van een dergelijk programma te vergroten. Dit proefschrift en andere studies laten zien dat de screeningprogramma's voor HCV infectie tot nu toe slechts een klein deel van het wereldwijd geschatte aantal HCV-infecties hebben geïdentificeerd. Het illustreert dat er niet één strategie is die alle doelgroepen kan bereiken en dat verschillende strategieën en grootschalige progamma's nodig zijn.

Op basis van de studies en discussie in dit proefschrift presenteren we de volgende aanbevelingen:

- Screeningprogramma's zouden systematisch hun kenmerken en resultaten moeten rapporteren, inclusief de uitkomsten van klinische follow-up. Idealiter zouden zij vergelijkingsgroepen moeten gebruiken om de effectiviteit van hun screeningstrategie te kunnen beoordelen.
- Internet-screeningprogramma's zouden hulpmiddelen en meerdere strategieën moeten gebruiken om het testgedrag te vergroten, zoals herinneringsberichten, een duidelijk omschreven en relatief krappe deadline voor bloedtesten, nabijgelegen testlocaties en een oplossing voor technische problemen. Daarnaast zouden deze programma's gebruik moeten maken van op theorie gebaseerde persuasieve communicatiestrategieën gericht op psychosociale determinanten van testen op HCV infectie.
- Screeningprogramma's zouden nationale media en grootschalige campagnes moeten gebruiken om hun bereik te maximaliseren.
- Screeningprogramma's op locatie voor eerste generatie migranten uit endemische landen voor HCV en/of HBV infectie zouden gelijktijdige screening voor zowel HCV en HBV infectie moeten aanbieden.
- Niet-invasieve testen voor HBV en HCV infectie zouden kunnen worden overwogen voor outreach- en internet-screeningprogramma's. Zelftests kunnen een veelbelovend instrument zijn voor toekomstige screeningprogramma's.
- Toekomstig onderzoek zou verder inzicht moeten geven in de ongediagnosticeerde populatie per risicogroep voor HCV infectie en zou de kosteneffectiviteit van verschillende strategieën van screening moeten vergelijken.
- Ad-hoc HCV screeningprogramma's voor migranten zouden moeten worden stopgezet.
  De huidige kennis over de effectiviteit van screeningprogramma's moet worden samengevat, resulterend in een uniform nationaal actieplan waarin verschillende screeningstrategieën worden gecombineerd.

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Deze typologie is ook losgelaten op mensen in het algemeen: "*The Ant type of people: they never do anyone any harm but they exist totally for their own living and pay no attention to others' well being. The Spider type of people: they exist to feed their self-interest alone at the expense of others and harm others in the process. The Bee type of people: they pursue their own interest and well being but in the process always help others as well.*"

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Freke

BIOGRAFIE

Freke Zuure werd geboren op 21 maart 1980 in Naarden. In juni 1998 behaalde zij haar gymnasium diploma aan openbare scholengemeenschap De Meergronden in Almere Haven. Daarna vertrok zij voor een jaar naar Australië en Nieuw-Zeeland om te reizen en te werken. Direct na terugkomst in Nederland verhuisde Freke naar Enschede om "Toegepaste communicatiewetenschap" te gaan studeren aan de Universiteit Twente met als hoofdrichting gezondheidscommunicatie en als minor kennisoverdracht in bedrijfs- en onderwijssituaties. Deze studie rondde zij in november 2005 af met een afstudeeronderzoek naar het gebruik van internet voor gezondheidsdoeleinden.

In februari 2006 startte Freke met haar promotieonderzoek op de afdeling Onderzoek van de GGD Amsterdam, waarvan dit proefschrift het resultaat is. Tijdens deze periode heeft zij gewerkt aan diverse onderzoeken en projecten op het gebied van hepatitis B, hepatitis C, hiv en eHealth. Hiernaast voerde ze ook andere werkzaamheden uit, onder andere als communicatieadviseur voor het Sarphati Initiatief, de Academische Werkplaats Publieke Gezondheid regio Noord-Holland en Flevoland (voorheen: Academische Werkplaats Publieke Gezondheid GGD Amsterdam – AMC). In 2012 vergaarde Freke samen met Jannie van der Helm financiering voor de ontwikkeling en evaluatie van een trial waarin zelftests voor hiv in combinatie met begeleiding via internet worden aangeboden aan hoogrisicogroepen voor hiv infectie die zich niet elders laten testen. Sinds juli 2012 is zij als postdoc werkzaam op de afdeling Onderzoek van de GGD Amsterdam.

(C=hep C)