Case finding strategies for hepatitis C infection

– Charles Helsper –

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Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht.

Thesis. University Utrecht, Faculty of medicine, with a summary in Dutch.

ISBN/EAN:	9789461082428
Design & layout:	www.planpuur.nl
Print:	Drukkerij Gildeprint, Enschede

The studies presented in this thesis were financially supported by

- ZonMw, The Netherlands Organisation for Health Research and Development

The printing of this thesis was financially supported by

- SBOH, employer of GP trainees in the Netherlands

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Opsporingsstrategieën voor hepatitis C infectie (met een samenvatting in het Nederlands)

Proefschrift
ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op
donderdag 15 december 2011 des ochtends te 10.30 uur

door:
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geboren op 9 maart 1980
te Pullman, Verenigde Staten van Amerika

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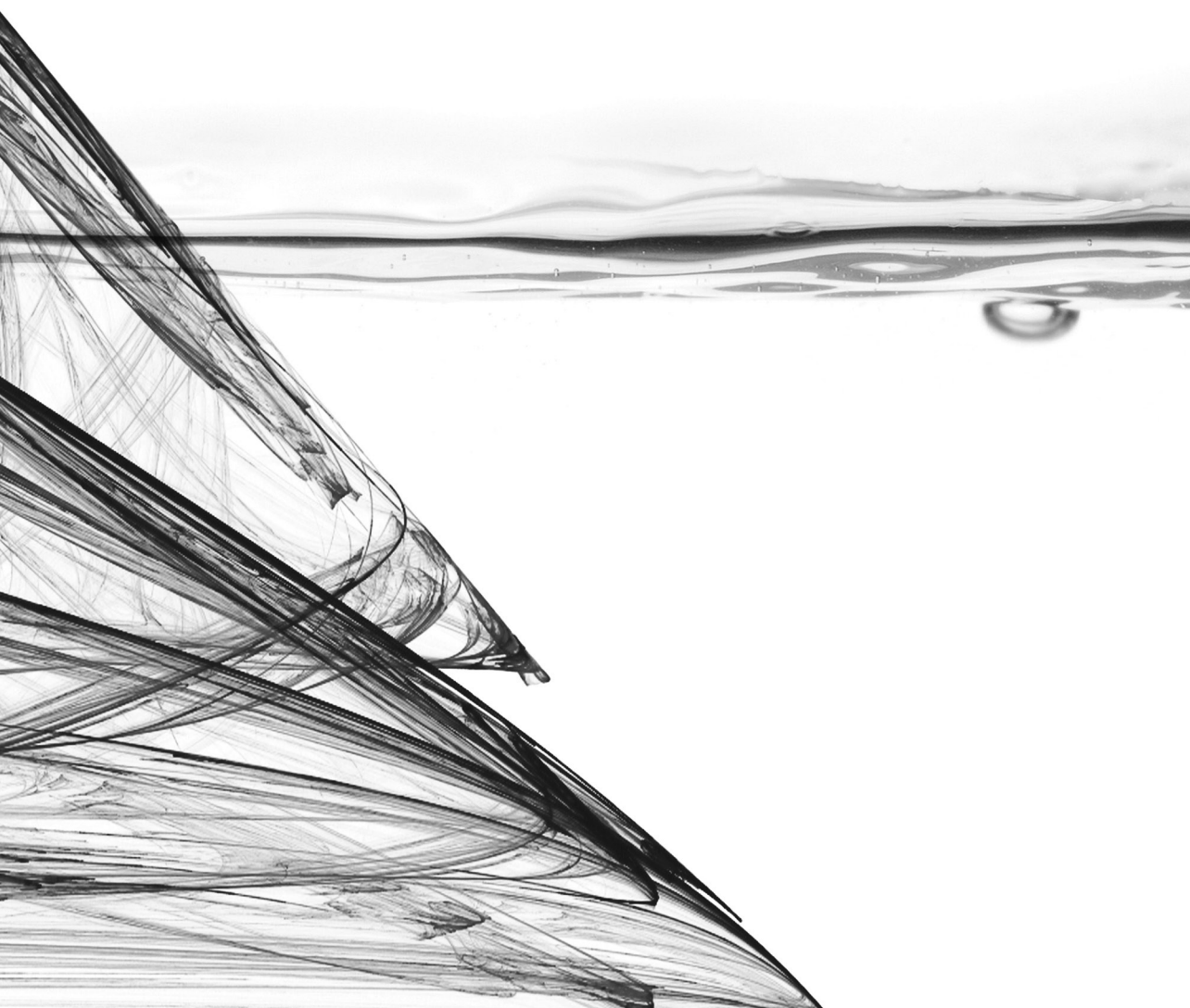
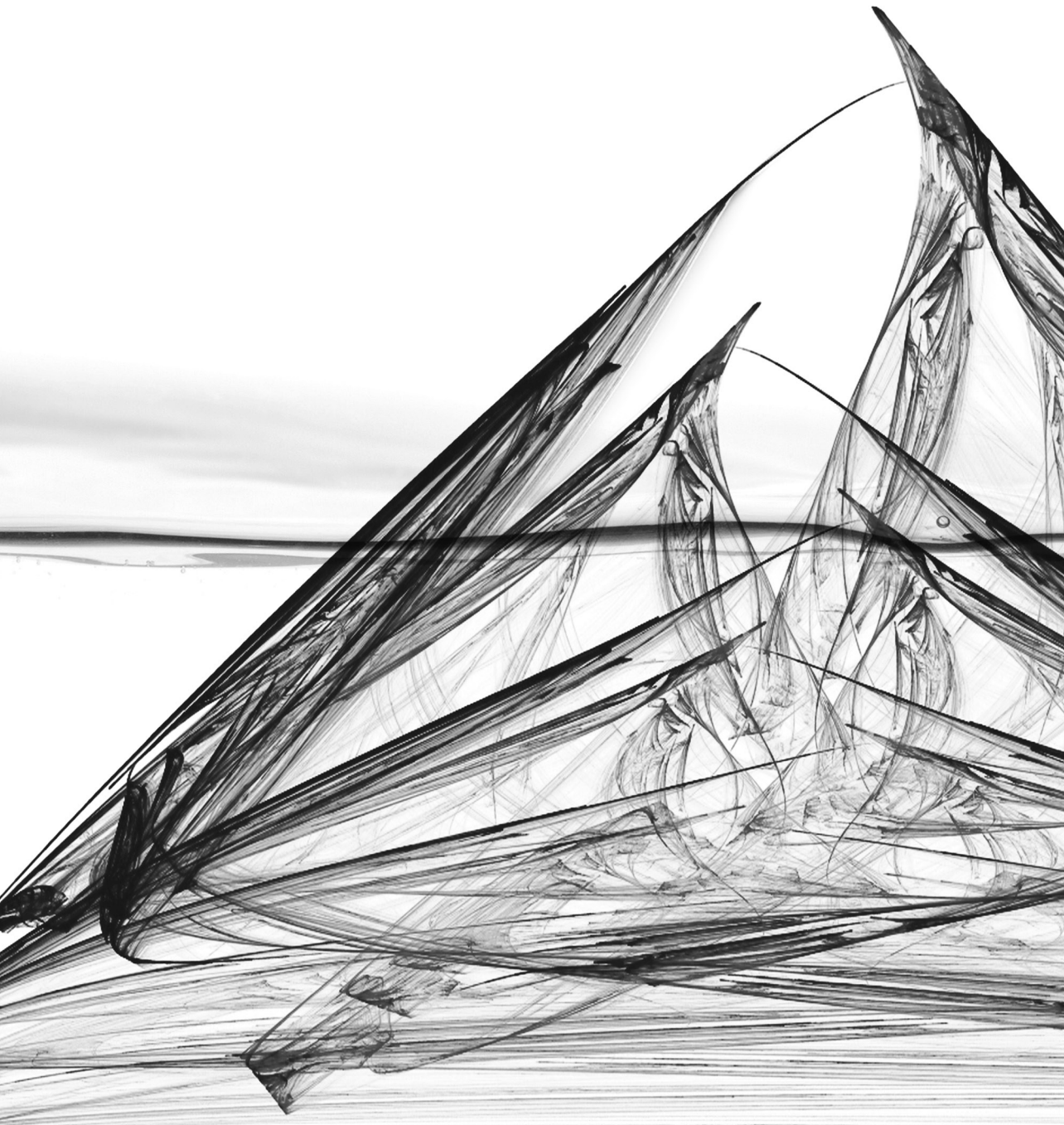
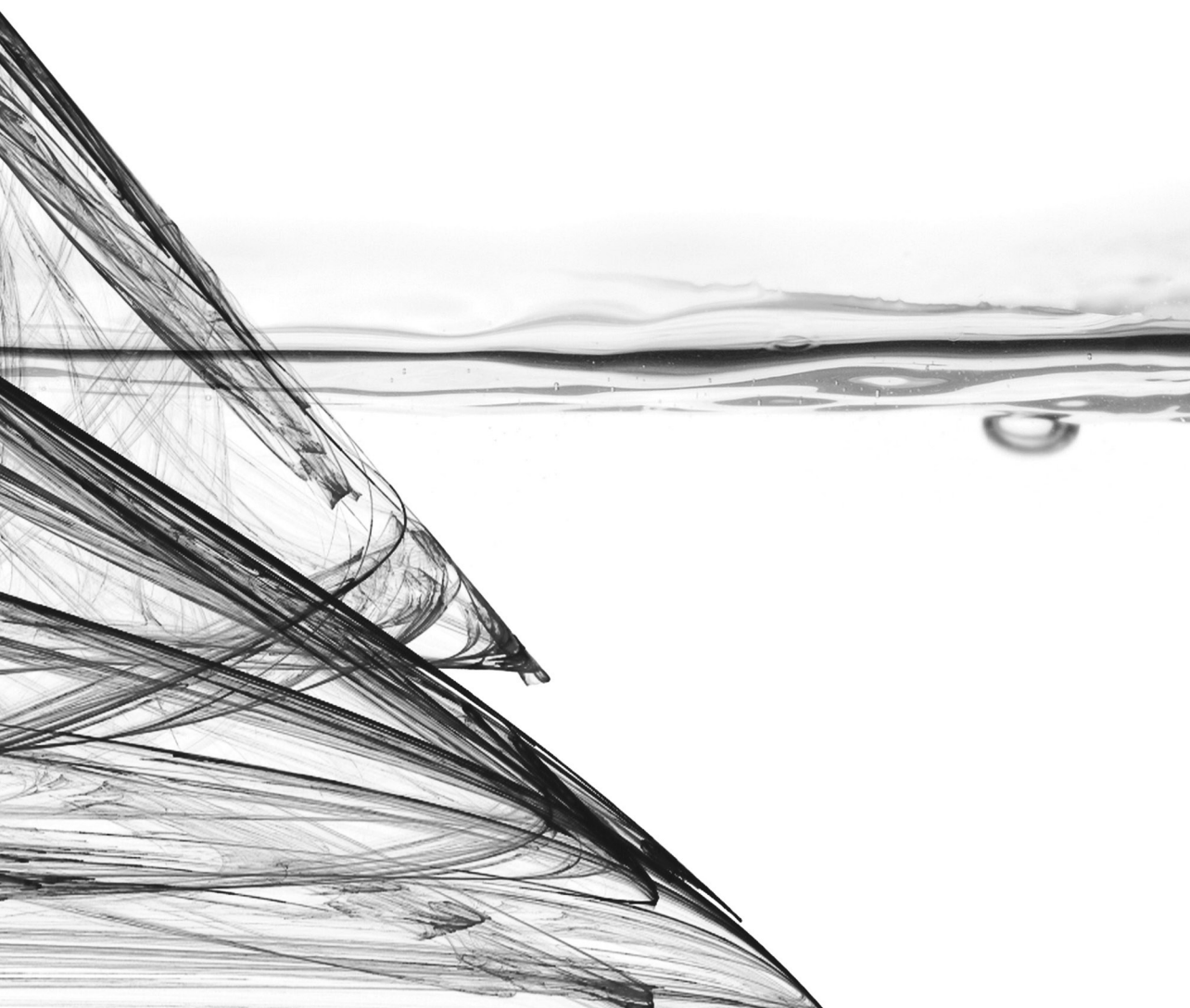




Chapter 1

General introduction



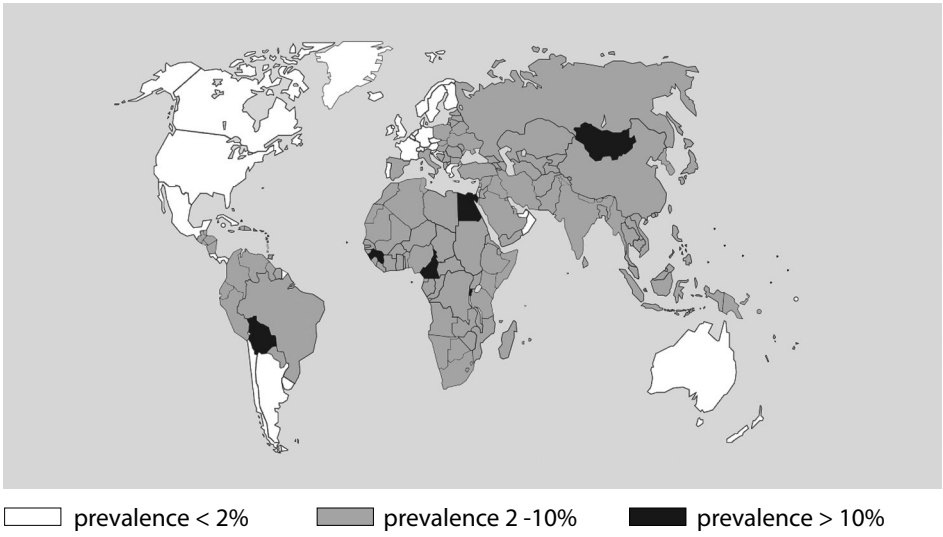
General introduction

Hepatitis C virus infection (HCV) is a viral liver disease. The virus was discovered as recently as 1989. Before then, it was probably behind the majority of cases of a condition known at that time as 'non-A, non-B hepatitis'.[1] At present, it is estimated that 123 to 170 million people are infected with HCV globally.[2,3] In Europe (including Russia) the number of HCV carriers is estimated at 11.3 to 14.7 million with varying prevalence rates of approximately 0.5% in North-West Europe to over 7% in parts of South-East Europe.[4] The prevalence in the Netherlands is estimated to be between 0.1% and 0.4% and up to 0.6% in the population of highly urbanized areas.[5-7] The estimated diagnosis rate varies considerably in Europe from 2.7% in Poland to 80% in Sweden.[4] In the Netherlands rough estimates indicate that only a quarter of the HCV carriers has been diagnosed.[5,8] The main reason for this is that HCV infection generally does not cause clinical symptoms until the stage of substantial liver damage. As a consequence, identification is often delayed until the serious long-term complications develop. The rates of chronic infection and long-term complications depend on several patient- and disease related factors such as gender, race, age and the presence of co-infections.[9] On average, 25 to 30% of those who are infected clear the virus naturally. This usually happens within six months.[10] The remaining patients develop a chronic infection, which can lead to serious long-term complications. Approximately 20 to 30% develops liver cirrhosis in 20 to 30 years. Annually, 1 to 5% of the patients with cirrhosis develops hepatocellular carcinoma.[9,11] As a consequence, HCV is considered responsible for 50% to 76% of all liver cancer cases and two-thirds of all liver transplants in the Western world.[12]

The infectious pathway of HCV is generally considered to be strictly blood-bound. Estimated infection rates after percutaneous exposure differ from 0 to 10%, depending on the number of virus particles in the infected blood and the volume of the inoculum.[13-16] This blood-bound transmission rate is approximately tenfold that of HIV.[17-19] Based on the infectious pathway of HCV, several high-risk groups have been defined. The risk group with the highest HCV prevalence is injecting drug users (IDU). In this group, the estimated HCV prevalence is 60 to 80%.[20] Non-injecting hard drug users are also at increased risk. Infectious pathways in this group remain unclear but are hypothesized to take place through blood to blood contact resulting from the use of drug-related equipment, household transmission (such as the shared use of toothbrushes or shaving instruments) or sexual contact with mucosal damage. Injecting drug use may well be underreported in this group.[21,22] As a result, the prevalence of HCV infection in non-injecting hard drug users is estimated to be 2.3 to 35.3%.[22] In the Netherlands this prevalence is estimated at approximately 6%.[21] A second risk group which is large in number but relatively low in HCV prevalence, is that of patients who have received blood, blood-products, haemodialysis or organ transplants.[23] Starting from 1992 these transfusion

products are tested for HCV in the Western world. In many developing countries this is still not routine practice. Prevalence rates in this risk group differ depending on the amount and the type of transfusion products received and the local prevalence and hygiene. Those who did not receive transfusions, but had their skin pierced otherwise in non-Western countries are also at increased risk of HCV. This includes both travellers and immigrants. Risk of infection depends on the type of piercing, the local infection rate and the hygienic conditions of the procedure. In a few countries, HCV can be called a true epidemic with prevalences of over 10% (figure 1). Egypt is the country with the highest infection rate, with prevalences of over 20% in some regions. This is the result of parenteral anti-schistosomal therapy (PAT) with inadequately sterilized injection material which was used until the 1980s and caused one of the largest known iatrogenic outbreaks of an infectious disease. [24] Other countries with a prevalence of over 10% are Mongolia, Bolivia, Guinea, Rwanda, Burundi and Cameroon. [2] First generation immigrants from these countries are considered a risk group, irrespective of known skin piercings.

Figure 1. Estimated prevalence of HCV



Estimated prevalence of HCV, based on: Hepatitis C: global prevalence. Wkly Epidemiol Rec 1997; 72(46):341-344. WHO Global burden of Disease study 2000, International travel and Health 2005, supplemented with literature on local prevalences

Mother-to-child transmission rates are 4 to 7% in case the mother has an active HCV infection. This is 4 to 5 times higher if the mother is also HIV infected.[25] Even though household transmission is uncommon, skin or mucosa piercings have also led to household infections in family members of HCV carriers through the shared use of, for instance, a toothbrush or shaving equipment.[23,26,27]

Most of the HCV carriers diagnosed are patients with a chronic infection who acquired the infection some time ago. An exception to this are HIV-positive men who have sex with men. In this relatively new risk group, recent epidemics of HCV infection have been found.[28-32] This is the only group in which HCV is truly considered a sexually transmittable disease. In heterosexual partners, the annual HCV transmission rate is expected to be between 0 and 0.6% for monogamous long-term relationships and between 0.4 and 1.8% for those with multiple partners. It is unclear whether these transmissions were sexual or if they were (partially) the result of household transmissions.[33] Evidence for household transmissions however is weak.[23,34] The origin of infection remains unknown for approximately 30% of the chronically HCV-infected population and the search for modes of transmission is ongoing. Even though this has led to some clues for other alternative routes of transmission, the number of HCV patients for whom no infectious pathway can be determined remains substantial.[34]

There are 7 known genotypes of hepatitis C. In the Netherlands, over 98% of patients are infected with genotype 1 to 4.[27,35] These genotypes are also the most prevalent in the rest of Europe. In North America genotypes 1 to 3 are most common, whereas genotype 4 and 5 are found in Africa and the Middle East. Genotype 6 is mainly seen in Asia. Genotype 7 has only recently been discovered and probably originates from Central Africa.[36,37]

In the past decade, success rates for HCV treatment have improved substantially. At present, approximately 50% of those infected with HCV genotype 1 or 4 and 80% of those with genotype 2 or 3 can be cured. To achieve cure (called 'sustained viral response' or SVR) the average treatment duration required varies from 48 weeks for those with genotype 1 and 4 and 24 weeks for those infected with HCV genotype 2 and 3.[38] In the near future, further improvement of treatment is expected with higher cure rates after a shorter and less burdensome treatment.[39-43]

In contrast to improved treatment success rates, the detection rate of HCV patients remains disappointing. There are several reasons for the underdiagnosis of HCV. The largest barrier for timely case finding is the lack of clinical symptoms in patients with both acute and chronic HCV infection. [11] This has several consequences. First and foremost, the absence of clinical symptoms makes patients simply unaware of infection. Since these patients do not consult, HCV testing merely takes place in patients consulting with clinical signs caused by progressive disease, or in patients with a recognized increased

risk. The latter mainly occurs on the initiative of the physician, who is most likely to practice in primary- or addiction care. The awareness of HCV risk among general practitioners (GPs), however, is low. Even though there are on average approximately 7 undiagnosed HCV patients per GP-practice in the Netherlands, clinical knowledge about hepatitis C among GPs has been demonstrated to be below standard.[44-49] Patients at risk are not tested because GPs are unfamiliar with risk groups, or have incorrect beliefs about the inadequacy of HCV treatment.[45,48,49] In addition, even if patients with HCV are detected, 50% is not referred, mostly for incorrect reasons.[50]
In addiction care, knowledge and awareness of HCV are generally more advanced than in primary care but there is still room for improvement.[51] However, in addiction care several other barriers for HCV case finding, mostly patient related, have been identified. A lack of information has led to misconceptions of HCV among hard drug users. HCV is frequently perceived as relatively benign due to the absence of symptoms. In addition, fear of investigations and treatment and limited access to testing and referral provide serious barriers for case finding and treatment.[52]
Current strategies have not overcome most of these barriers for HCV case finding. Therefore, there is a need for the development and evaluation of new approaches in HCV detection.[53-55]

In summary, hepatitis C is a serious disease with severe long-term complications. With improvement of treatment in the past decades, HCV has become a curable disease for most patients. With this change in disease perspective, the urgency for tracking patients with HCV infection has grown. Despite the fact that important risk factors have been identified, the number of HCV patients traced remains disappointing leaving most of the HCV infected patients undiagnosed. Therefore, there is a major challenge in improving strategies to identify those at risk of HCV.

Aims of the thesis
The aim of this thesis is to improve case finding of hepatitis C by evaluating the effectiveness and cost-effectiveness of new case finding strategies developed for public health and primary care practice.

Outline of the thesis
To achieve this aim we performed several studies:

- Chapter 2 describes the results of the assessments of two pilot HCV campaigns, each comparing two different strategies for the detection of HCV patients. Chapter 2.1 shows the effectiveness of two strategies for a mass media campaign aimed at risk groups in the general public. In both strategies, mass media are used to reach risk groups in the general public. In the first strategy, no support is provided for medical

professionals. In the second strategy, the same mass media campaign is used but in addition a support campaign for primary care is implemented complementary to the mass media campaign. Chapter 2.2 describes the effectiveness of two strategies aimed at informing and testing those at risk in the hard drug using population (HDU). In both strategies, information on HCV is made available in addiction care institutions for attending HDU through posters and brochures. In one strategy, consultation and testing only took place when requested by the HDU. In the other strategy, the same information was provided but visiting HDU were actively approached by the addiction care workers and offered HCV consultation and testing on the spot.

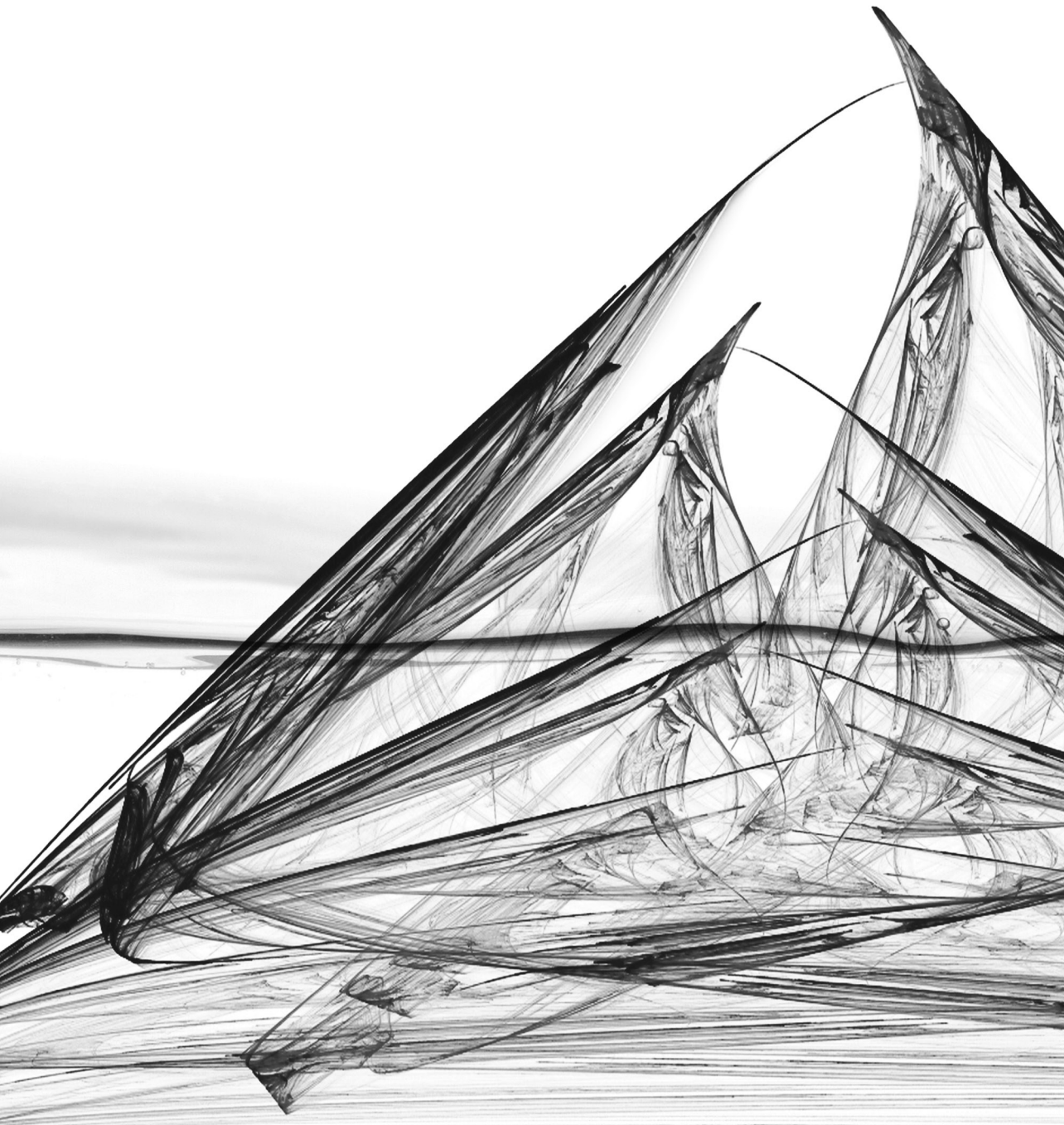
- Chapter 3 discusses the economical burden of different campaign strategies. Chapter 3.1 addresses the cost-effectiveness of the main strategies which were discussed in Chapter 2. Since the case finding strategies result in an increased need for treatment and consequently induce treatment-related costs, these are discussed in Chapter 3.2. This chapter provides an overview of the present costs of treatment in the Netherlands. Based on the findings described in the studies in Chapter 2, a national hepatitis C campaign was implemented in the Netherlands. Chapter 3.3 describes the effects and cost-effectiveness of the different strategies used in this national hepatitis C campaign.
- Chapter 4 was needed since it could not be expected that the aforementioned strategies would succeed in finding all hidden hepatitis C carriers in the Netherlands. This chapter describes the effectiveness of a new case finding strategy, based on elevations of the alanine aminotransferase (ALT) which are frequently found in daily primary care practice.
- Chapter 5 discusses the findings of the studies presented in chapter 2 to 4. This 'General discussion' summarizes the lessons learned from this thesis and addresses implications for current and future practice.

Reference List

1. Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science 1989; 244(4902):359-362.
2. Hepatitis C: global prevalence. Wkly Epidemiol Rec 1997; 72(46):341-344.
3. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis 2005; 5(9):558-567.
4. Cornberg M, Razavi HA, Alberti A, Bernasconi E, Buti M, Cooper C et al. A systematic review of hepatitis C virus epidemiology in Europe, Canada and Israel. Liver Int 2011; 31 Suppl 2:30-60.
5. Health Council of the Netherlands: Committee on hepatitis C. Detection and treatment of people with hepatitis C. 1997/19. 1997. Rijswijk.
6. Slavenburg S, Verduyn-Lunel FM, Hermsen JT, Melchers WJ, te Morsche RH, Drenth JP. Prevalence of hepatitis C in the general population in the Netherlands. Neth J Med 2008; 66(1):13-17.
7. Baaten GG, Sonder GJ, Dukers NH, Coutinho RA, van den Hoek JA. Population-based study on the seroprevalence of hepatitis A, B, and C virus infection in Amsterdam, 2004. J Med Virol 2007; 79(12):1802-1810.
8. Kretzschmar MEE. De prevalentie van hepatitis C in Nederland [The prevalence of hepatitis C in the Netherlands] Noted for ministry of VWS-IGZ. notitie RIVM . 2-12-2004.
9. Seeff LB. Natural history of chronic hepatitis C. Hepatology 2002; 36(5 Suppl 1):S35-S46.
10. Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. J Viral Hepat 2006; 13(1):34-41.
11. Lauer GM, Walker BD. Hepatitis C virus infection. N Engl J Med 2001; 345(1):41-52.
12. World Health Organization (WHO). State of the art of vaccine research and development. Report number WHO/IVB/05.XX. 2011.
13. Washer P. Hepatitis C: transmission, treatment and occupational risk. Nurs Stand 2001; 15(40):43-46.
14. Sulkowski MS, Ray SC, Thomas DL. Needlestick transmission of hepatitis C. JAMA 2002; 287(18):2406-2413.
15. Jagger J, Puro V, De Carli G. Occupational transmission of hepatitis C virus. JAMA 2002; 288(12):1469-1471.
16. Corey KE, Servoss JC, Casson DR, Kim AY, Robbins GK, Franzini J et al. Pilot study of postexposure prophylaxis for hepatitis C virus in healthcare workers. Infect Control Hosp Epidemiol 2009; 30(10):1000-1005.
17. Bell DM. Occupational risk of human immunodeficiency virus infection in healthcare workers: an overview. Am J Med 1997; 102(5B):9-15.
18. Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis. MMWR Recomm Rep 2001; 50(RR-11):1-52.
19. Coutinho RA. HIV and hepatitis C among injecting drug users. BMJ 1998; 317(7156):424-425.
20. Nelson PK, Mathers BM, Cowie B, Hagan H, Des JD, Horyniak D et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. Lancet 2011.
21. van den Berg CH, van de Laar TJ, Kok A, Zuure FR, Coutinho RA, Prins M. Never injected, but hepatitis C virus-infected: a study among self-declared never-injecting drug users from the Amsterdam Cohort Studies. J Viral Hepat 2009; 16(8):568-577.
22. Scheinmann R, Hagan H, Lelutiu-Weinberger C, Stern R, Des J, Flom PL et al. Non-injection drug use and Hepatitis C Virus: a systematic review. Drug Alcohol Depend 2007; 89(1):1-12.
23. van de Laar TJ, Koppelman MH, van der Bij AK, Zaaijer HL, Cuijpers HT, van der Poel CL et al. Diversity and origin of hepatitis C virus infection among unpaid blood donors in the Netherlands. Transfusion 2006; 46(10):1719-1728.

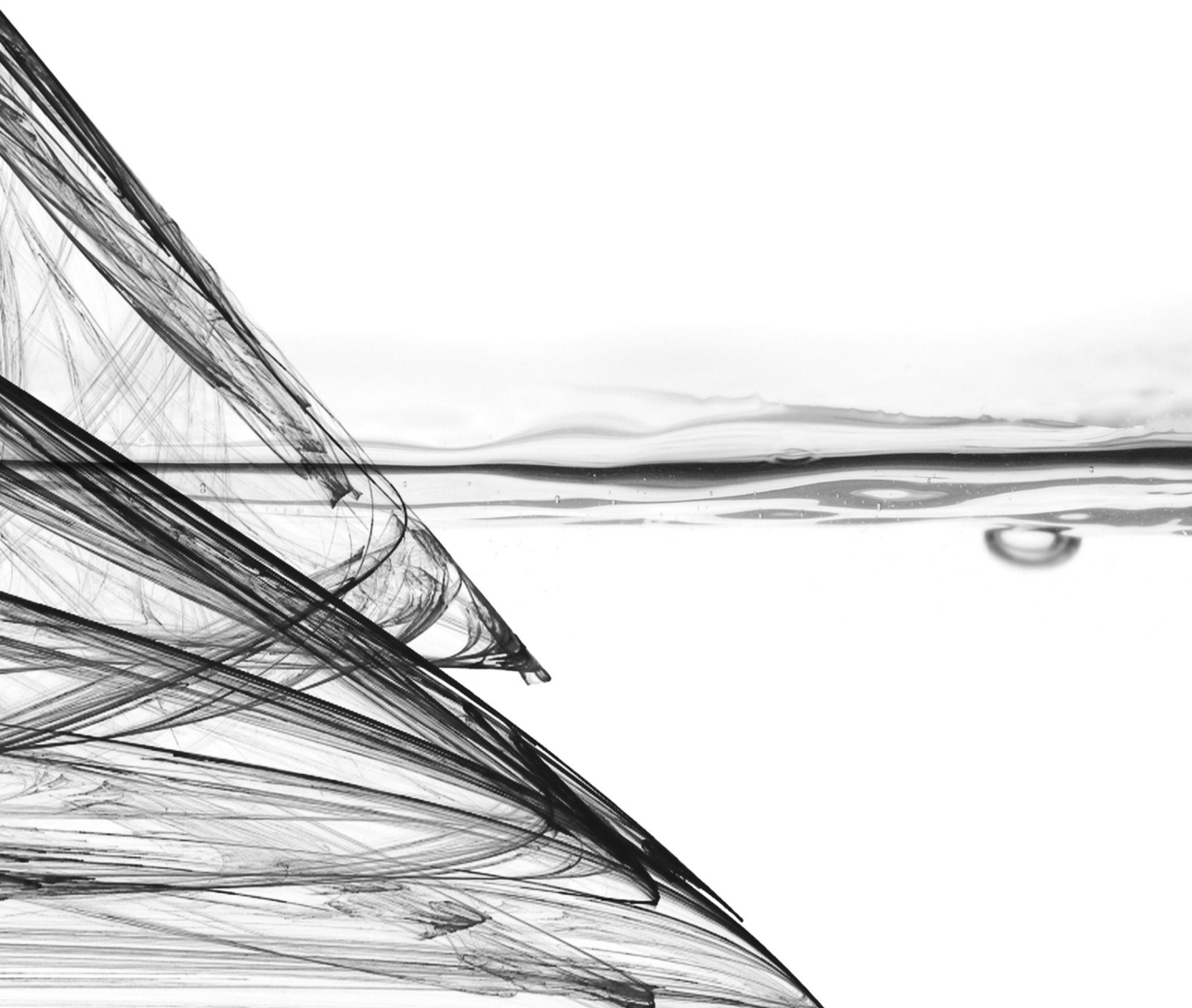
24. Frank C, Mohamed MK, Strickland GT, Lavanchy D, Arthur RR, Magder LS et al. The role of parenteral antischistosomal therapy in the spread of hepatitis C virus in Egypt. Lancet 2000; 355(9207):887-891.
25. Roberts EA, Yeung L. Maternal-infant transmission of hepatitis C virus infection. Hepatology 2002; 36(5 Suppl 1):S106-S113.
26. Clarke A, Kulasegaram R. Hepatitis C transmission -- where are we now? Int J STD AIDS 2006; 17(2):74-80.
27. de Vries MJ, te RB, van Nieuwkerk CM. Transmission of hepatitis C genotypes in the Netherlands amongst recently genotyped patients. Neth J Med 2008; 66(1):40-41.
28. Urbanus AT, van de Laar TJ, Stolte IG, Schinkel J, Heijman T, Coutinho RA et al. Hepatitis C virus infections among HIV-infected men who have sex with men: an expanding epidemic. AIDS 2009; 23(12):F1-F7.
29. van de Laar TJ, van der Bij AK, Prins M, Bruisten SM, Brinkman K, Ruys TA et al. Increase in HCV incidence among men who have sex with men in Amsterdam most likely caused by sexual transmission. J Infect Dis 2007; 196(2):230-238.
30. van de Laar T., Pybus O, Bruisten S, Brown D, Nelson M, Bhagani S et al. Evidence of a large, international network of HCV transmission in HIV-positive men who have sex with men. Gastroenterology 2009; 136(5):1609-1617.
31. van de Laar TJ, Matthews GV, Prins M, Danta M. Acute hepatitis C in HIV-infected men who have sex with men: an emerging sexually transmitted infection. AIDS 2010; 24(12):1799-1812.
32. Montoya-Ferrer A, Fierer DS, varez-Alvarez B, de GM, Fernandez-Guerrero ML. Acute Hepatitis C Outbreak among HIV-infected Men, Madrid, Spain. Emerg Infect Dis 2011; 17(8):1560-1562.
33. Terrault NA. Sexual activity as a risk factor for hepatitis C. Hepatology 2002; 36(5 Suppl 1):S99-105.
34. Karmochkine M, Carrat F, Dos SO, Cacoub P, Raguin G. A case-control study of risk factors for hepatitis C infection in patients with unexplained routes of infection. J Viral Hepat 2006; 13(11):775-782.
35. de Vries MJ, te RB, van Nieuwkerk CM. Genotype distribution amongst hepatitis C patients in The Netherlands. Neth J Med 2006; 64(4):109-113.
36. Murphy D, Chamberland J, Dandavino R, SE. A new genotype of hepatitis C virus originating from central Africa. Hepatology. . Hepatology 2007; 46(623A).
37. Simmonds P, Bukh J, Combet C, Deleage G, Enomoto N, Feinstone S et al. Consensus proposals for a unified system of nomenclature of hepatitis C virus genotypes. Hepatology 2005; 42(4):962-973.
38. Manns MP, Foster GR, Rockstroh JK, Zeuzem S, Zoulim F, Houghton M. The way forward in HCV treatment--finding the right path. Nat Rev Drug Discov 2007; 6(12):991-1000.
39. Soriano V, Peters MG, Zeuzem S. New therapies for hepatitis C virus infection. Clin Infect Dis 2009; 48(3):313-320.
40. Zeuzem S. Interferon-based therapy for chronic hepatitis C: current and future perspectives. Nat Clin Pract Gastroenterol Hepatol 2008; 5(11):610-622.
41. Jensen DM. A new era of hepatitis C therapy begins. N Engl J Med 2011; 364(13):1272-1274.
42. Poordad F, McCone J, Jr., Bacon BR, Bruno S, Manns MP, Sulkowski MS et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 2011; 364(13):1195-1206.
43. Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S et al. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med 2011; 364(13):1207-1217.
44. Netherlands Institute of Health Services Research (NIVEL). GP registration numbers - 2010 survey [in Dutch] (Cijfers uit de registratie van huisartsen - peiling 2010).
45. Ferrante JM, Winston DG, Chen PH, de la Torre AN. Family physicians' knowledge and screening of chronic hepatitis and liver cancer. Fam Med 2008; 40(5):345-351.
46. Frazer K, Glacken M, Coughlan B, Staines A, Daly L. Hepatitis C virus infection in primary care: survey of registered nurses' knowledge and access to information. J Adv Nurs 2011; 67(2):327-339.

47. Evon DM, Simpson KM, Esserman D, Verma A, Smith S, Fried MW. Barriers to accessing care in patients with chronic hepatitis C: the impact of depression. Aliment Pharmacol Ther 2010; 32(9):1163-1173.
48. Coppola AG, Karakousis PC, Metz DC, Go MF, Mhokashi M, Howden CW et al. Hepatitis C knowledge among primary care residents: is our teaching adequate for the times? Am J Gastroenterol 2004; 99(9):1720-1725.
49. D'Souza RF, Glynn MJ, Alstead E, Osonayo C, Foster GR. Knowledge of chronic hepatitis C among East London primary care physicians following the Department of Health's educational campaign. QJM 2004; 97(6):331-336.
50. de Jong DJ, de Vries MJ, Boonman-de Winter LJ, van WP. Referral of hepatitis C virus seropositive patients in primary care in the Netherlands. Neth J Med 2008; 66(1):42-43.
51. Doab A, Treloar C, Dore GJ. Knowledge and attitudes about treatment for hepatitis C virus infection and barriers to treatment among current injection drug users in Australia. Clin Infect Dis 2005; 40 Suppl 5:S313-S320.
52. Swan D, Long J, Carr O, Flanagan J, Irish H, Keating S et al. Barriers to and facilitators of hepatitis C testing, management, and treatment among current and former injecting drug users: a qualitative exploration. AIDS Patient Care STDS 2010; 24(12):753-762.
53. Sroczynski G, Esteban E, Conrads-Frank A, Schwarzer R, Muhlberger N, Wright D et al. Long-term effectiveness and cost-effectiveness of screening for hepatitis C virus infection. Eur J Public Health 2009; 19(3):245-253.
54. Smith BJ, Bauman AE, Chen J, Loveday S, Costello M, Mackie B et al. Hepatitis C in Australia: impact of a mass media campaign. Am J Prev Med 2006; 31(6):492-498.
55. Colvin HM, Mitchel AE, Committee on the Prevention and Control of Viral Hepatitis Infections, Institute of Medicine. Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C. 2010.



Chapter 2

Effectiveness of case finding strategies



Chapter 2.1

A support programme for primary care leads to substantial improvements in the effectiveness of a public hepatitis C campaign

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Family Practice, 2010 Jun;27(3):328-32

Abstract

Introduction: Because of its lack of clinical signs, the detection of hepatitis C virus (HCV) infection in the Netherlands remains suboptimal. Therefore, the Dutch Health Council proposed an HCV campaign aimed to inform the general public and motivate people at risk to seek medical advice. Because knowledge and awareness of HCV infection is low among primary care workers, the implementation of a support programme for primary care complementary to a HCV campaign seems appropriate.
Objective. To evaluate the added value of a support programme for primary care complementary to a public HCV campaign.

Methods: We performed a non-randomized controlled intervention study. In two similar regions, a public HCV campaign was organized. In the intervention region, an additional support for primary care was provided by means of brochures, short courses and informative visits.

Results: In the intervention region, the proportional increase in anti-HCV tests was 3.02 (57–172 tests). In the control region, this increase was 1.36 (86–118 tests). In the intervention region, the increase in positive anti-HCV tests was 1.7% (95% confidence interval (CI): –0.2% to 3.7%). In the control region, this number decreased by 0.9% (95% CI: –4.1% to 2.3%).

Conclusions: The addition of primary care practice support leads to considerable improvements in medical consciousness regarding HCV infection in primary care. Even though the positive effect on case finding cannot be indisputably demonstrated due to low prevalence, our results indicate such a positive effect. Therefore, future campaigns aimed at hepatitis C should invariably implement additional support for primary care to improve diagnostic uptake and optimize case finding.

Introduction

Infection with hepatitis C virus (HCV) is a global problem, affecting approximately 3% of the world's population and between 0.1% and 0.4% of the Dutch population.[1–4] Because the disease often presents without typical clinical signs, it is estimated that only a quarter of the hepatitis C carriers in the Netherlands has been diagnosed.[3–5] Acute HCV infection leads to chronic hepatitis in 80% of cases of which 20% develop liver cirrhosis after 20–30 years. Of those with cirrhosis, 1%–4% develops hepatocellular cancer annually. HCV is responsible for 50%–76% of all cases of liver cancer and two-thirds of all liver transplants in the western world.[1,5,6] In the past decade, treatment has improved dramatically with regard to success rate and treatment duration. Today 40%–50% of patients carrying HCV genotype type 1 and 4 and >75% of patients carrying genotype 2 and 3 can be cured with antiviral treatment, which lasts a maximum of 48 weeks.[6–9] Infection with HCV can only occur if blood–blood contact has taken place. The strictly blood-bound infectious pathway determines several risk groups that are seriously at risk of hepatitis C infection in present or past (Box 1).[3,10]

Box 1. Hepatitis C risk groups

The following groups have been identified as risk groups:[3,10]

- The (former) use of hard drugs, especially injecting drug use (IDU).
- First generation immigrants from countries with prevalences above 10%.[11] These countries are: Egypt, Burundi, Cameroon, Guinee, Bolivia, Mongolia and Rwanda.
- Travellers to countries with a prevalence above 2%[11], who have been exposed to:
  - any medical treatment during which the skin was pierced;
  - a tattoo or piercing;
  - ritual acts during which the skin was pierced such as circumcision or scarification;
  - working in a health care setting were blood contact is feasible.
- Recipients of blood products in western countries (Western Europe, USA, Australia) before 1992 and in non western countries up to today.
- Family members of hepatitis C positive patients who have lived with the carrier for more than one year.
- Professionals who have an occupational risk of blood contact with hepatitis C risk groups.
- Patients who have underwent dialysis and haemophiliacs are also at serious risk of having been infected with hepatitis C. Since testing these patients for hepatitis C is common practice, the hepatitis C campaign is not aimed at this risk group.

Because of the improved treatment possibilities and the low percentage of diagnosed patients, the Dutch government has initiated a hepatitis C public awareness campaign, which is to be implemented by The Netherlands Institute for Health Promotion (Nationaal Instituut voor Gezondheidsbevordering en Ziektepreventie). This campaign aims to increase public awareness of hepatitis C and stimulates those at increased risk of HCV infection to consult their GP or the regional Public Health Service (Gemeentelijke Gezondheidsdienst) for testing and, if positive, referral for treatment.[12]

GPs are expected to play a leading role in the implementation of this campaign through individual risk assessment and testing of those who are alerted by the campaign or identified in routine practice. However, awareness of hepatitis C among GPs is traditionally low in the Netherlands. In addition, a lack of knowledge about risk groups and infection pathways leads to varying attitudes, low test rates and inadequate referral for treatment.[13]

In order to make the campaign successful, knowledge of GPs about HCV needs to be improved. As previous studies have shown that educational sessions and practice support are an effective way to improve GP participation, these measures were incorporated in the HCV campaign.[3,12–17]

The objective of this study was to evaluate the added value of a complimentary primary care support programme to a public hepatitis C campaign, aimed at increasing awareness and identifying patients with hepatitis C infection.

Methods

Setting

A non-randomized controlled intervention study took place in primary care practices in two regions in the Netherlands, comparable in population and demography. The Amersfoort region, a central region with 110 GP practices, served as intervention region and Apeldoorn, a region in the east of the Netherlands with 109 practices, served as control region. All GPs who were not related to shelters for drug and alcohol addicts were included.

Intervention

In both regions, the public campaign was implemented, only in the intervention region the support programme for primary care was carried out. The public campaign consisted of radio and newspaper ads and information material distributed at public places, all aiming at increasing public awareness about HCV risk. The support programme for primary care consisted of three strategies:

1. Distribution of educational material regarding hepatitis C, specifically designed for the hepatitis C campaign. The material contained elaborate information on risk factors, treatment and testing of hepatitis C. It was developed in collaboration with the Dutch College of General Practitioners and distributed among all primary care practices.
2. Educational sessions for GPs on HCV management, both in small groups (5–12 GPs) and larger plenary courses (41 GPs).
3. In practice support for HCV risk assessment. Two practice facilitators were assigned to provide personal support during campaign to GPs assistants, primary care nurses and GPs, as a form of academic detailing.[17] During the visits of the practice facilitator, the risk groups of hepatitis C were emphasized.

The intervention period started with the public campaign and lasted for 4 months (October 2007 to January 2008). The training for GPs took place in the first month of the intervention period. The support programme for primary care was provided throughout the entire 4-month intervention period.

Outcome

Main outcome parameters were the number of anti-HCV tests requested by GPs and the number of positive tests.

Measurements and data collection

The regional laboratories of hospitals provided the data on anti-HCV tests. Positive tests were confirmed using polymerase chain reaction for HCV RNA testing.

Analysis

Results were compared between intervention and control group and corrected for the number of tests in the comparable time period before intervention. Analyses were performed using Excel and R statistical package. Crude proportion testing was used to determine 95% confidence intervals (95% CI).

This study did not require ethical approval since all collected data were entirely anonymous and without any resulting consequences for patients, GPs, GPs assistants or primary care nurses.

Results

GP participation

The short courses and the plenary course were attended by 70% of all GPs. The practice facilitators paid visits to all primary care practices twice during the intervention period.

Number of tests

In the intervention region, the number of anti-HCV tests increased from 57 tests in previous years to 172 tests during the intervention period. As shown in Table 1, this is a proportional increase in tests of 3.02. The average number of tests performed per GP increased from 0.5 tests in previous years to 1.6 tests during the campaign.

In the control region, the number of anti-HCV tests increased from 86 tests in previous years to 118 tests during the intervention period. As shown in Table 1, this is a proportional increase in tests of 1.36. The average number of tests performed per GP increased from 0.8 tests in previous years to 1.1 tests during the campaign.

Consequently, the increase in number of anti-HCV tests in the intervention region is 2.2 (95% CI: 1.5– 3.3) times as high as it is in the control region.

Number of positive tests

In the intervention region, the number of positive tests increased from an average of 0 out of 57 tests in similar periods in previous years to 3 out of 172 during the intervention period. This is an increase of 1.7% (95% CI: –0.2 to 3.7%) in the percentage of positive tests.

In the control region, the number of positive tests decreased from an average of 1.5 out of 86 in similar periods in previous years to 1 out of 118 during the intervention period. This is a decrease of 0.9% (95% CI: –4.1 to 2.3%).

Consequently, the difference in increase in the percentage of positive tests is 2.6% (95% CI: –0.7% to 5.8%).

Table 1 - Anti-HCV tests - October 2005 to January 2006, October 2006 to January 2007 and October 2007 to January 2008

Region	Mean Oct 05/06 to Jan 06/07		Oct 07 to Jan 08		Proportional increase in No of Anti-HCV tests	Increase in % positive (95% CI)
	No of Tests	Anti-HCV Positive	No of Tests	Anti-HCV Positive		
Intervention	57	0 (0%)	172	3 (1.7%)	3.02	1.7% (-0.2% to 3.7%)
Control	86	1.5 (1.7%)	118	1 (0.8%)	1.36	- 0.9% (-4.1 to 2.3%)

Discussion

Summary of findings

The addition of a support programme for primary care to a public hepatitis C campaign has a clearly positive effect on the number of anti-HCV tests, demonstrated by a more than 2-fold increase (2.2) as compared to a hepatitis C campaign without an additional support programme. The effect of additional support on case finding of possible HCV patients was not indisputable due to a low number of cases, but our results indicate that there is a positive effect on the percentage of positive HCV tests.

Based on the results from the hepatitis C campaign with and without the additional support programme, a rough estimation can be made of the effect of a national campaign. The campaign without a support programme would lead to an estimated increase in tests of approximately 3000 countrywide. If a support programme is implemented complementary to the campaign, the expected increase in number of anti-HCV tests is 7000, which would lead to the identification of an additional 146 HCV carriers countrywide.

Previous hepatitis C campaigns have proven to be potentially cost-effective (incremental cost-effectiveness ratio 20.000–25.000), when focussed on populations with elevated HCV prevalence.[18–20] To evaluate the cost-effectiveness of the different strategies used in this hepatitis C campaign, a country-specific model should be developed. The effect of this campaign however should not be expressed exclusively in the number of identified HCV carriers but should also consider the importance and moral obligation of informing

the general public and medical professionals of a very serious but curable disease.
The substantially larger increase in number of tests in the intervention region is likely to be the result of an increase in awareness among GPs and practice nurses. This confirms the conclusions in the literature that educational sessions, the employment of practice facilitators and information sent by mail are an effective way to improve participation of primary care practices in public campaigns.[14–17]
The positive effect of actively involving medical professionals in a hepatitis C campaign was also demonstrated by a campaign aimed at improving the diagnosis of hepatitis C among risk groups by training private practitioners (specialists and GPs) in France. This campaign demonstrated that informing and training private practitioners leads to a more active involvement, resulting in higher rates of HCV testing and improved case finding.[21] A study on the approach of risk groups by GPs, also performed in France, demonstrated not only an increase in HCV identification but also showed that a strategy aimed at improving the identification of HCV carriers exclusively based on case finding by the GP is, as a single intervention, not powerful enough to reach risk groups in need of HCV testing.[22]
A hepatitis C campaign in Australia has demonstrated that a public campaign aimed at informing the general public is an effective strategy to rise interest and improve general knowledge about hepatitis C.[23,24] The limited increase in the number of anti-HCV test in the control region shown in our study, indicates that this increase in awareness resulting from a public awareness campaign without additional support for primary care is moderate compared to a campaign including a support programme.
The findings of the above-mentioned studies support our conclusion that combining a public campaign with a support programme for primary care is vital in optimizing the increase in awareness and knowledge among risk groups, actively involving medical professionals and improving the conditions for increased awareness and case finding in a primary care setting.
Despite this substantial increase in the number of tests in the intervention region, the improvement in case finding is quite small (1.7%).
This is to be expected because

- It is plausible that before the campaign only patients with a very high risk were tested (e.g. injecting drug users). During the campaign, a large group of patients with a relatively low risk (e.g. blood recipients) will be activated to seek medical attention and therefore a low percentage of these patients will have a positive anti-HCV test.
- The prevalence of hepatitis C is expected to be subject to regional influences due to variations in the presence of HCV risk groups. Since the intervention and control region are only average sized cities in the Netherlands, this might have led to relatively low case finding in these areas.

- It is possible that the prevalence of hepatitis C in the Netherlands is lower in reality than the expected 0.1%–0.4%.[3,4] This would lead to low case finding in the whole of the Netherlands and insufficient numbers to show significant improvements in case finding in our data.

This was a pragmatic pilot study, evaluating the effect of an additional support programme for primary care on HCV awareness in which actual case finding was a matter of secondary importance. Ideally, we would have chosen an intervention and a control region sufficiently large to detect a predefined effect on case finding. Given the low prevalence of hepatitis C, this was not an attainable objective. Even though our results do indicate a positive effect of additional support for primary care on case finding, this pilot study was not powered to indisputably demonstrate this.
The increase of the population of the intervention and control region during the research period was very small (1.48% and 1.65%, respectively). Since there were no indications that the small increase in the population of both regions resulted in changes in the presence of hepatitis C risk groups, we considered the effect of population growth negligible for our results.
This study presents the results of a well-organized government-initiated hepatitis C campaign in two regions, which are of average size and population composition. Therefore, it provides pragmatic results and a realistic representation of the effects of a hepatitis C campaign in the Netherlands.

Conclusions

The addition of primary care practice support leads to considerable improvements in medical consciousness regarding hepatitis C in primary care. Even though the positive effect on case finding cannot be indisputably demonstrated due to low prevalence, our results do indicate such a positive effect. Therefore, future campaigns aimed at hepatitis C should invariably implement additional primary care practice support to improve diagnostic uptake and optimize hepatitis C case finding.

Acknowledgements
Funding was provided by: The Netherlands organization for health research and development (Nederlandse organisatie voor gezondheidsonderzoek en zorginnovatie) (Project number nr. 86000001).
Ethical approval: none. Conflicts of interest: none.

References

1. Anonymous, Hepatitis C: global prevalence, Wkly. Epidemiol. Rec. 1997;72: 341–348.
2. World Health Organization and Viral Hepatitis Prevention Board. Global surveillance and control of hepatitis C. J Viral Hepat 1999; 6: 35-47
3. Kok A, Zuure F R, Weegink C J, Coutinho R A, Prins M, Hepatitis C in the Netherlands; Hepatitis C in the Netherlands: sparse data on the current prevalence and the necessity for epidemiological studies and innovative methods for detecting infected individuals. Article in Dutch [Hepatitis C in Nederland: schaarse gegevens over actuele prevalentie en de noodzaak van epidemiologisch onderzoek en innovatieve opsporingsmethoden]. Ned Tijdschr Geneeskd. 2007 Oct 27;151(43):2367-2371
4. M. Kretschmar, The prevalence of hepatitis C in the Netherlands. Publication in Dutch [De prevalentie van hepatitis C in Nederland] notitie RIVM, 12-2004
5. The centre for infectious disease control. LCI protocol Hepatitis C, The Centre for Infectious Disease Control Netherlands. LCI/Gr, 2005, Bilthoven the Netherlands
6. Lauer G M, Walker B D. Hepatitis C virus infection. N Engl J Med 2001;345:41-52.
7. Poynard T, Yuen M F, Ratziu V, Lai C L. Viral hepatitis C. Lancet 2003 Dec 20;362(9401):2095-2100
8. Orlent H, Vrolijk J M, De Man R A, Schalm S W. The treatment of hepatitis C. Article in Dutch [Behandeling van hepatitis C]. Ned Tijdschr Geneeskd. 2003 Jun 21;147(25):1208-1213.
9. Manns M P, Foster G R, Rockstroh J K, Zeuzem S, Zoulim F, Houghton M. The way forward in HCV treatment -finding the right path. Nat Rev Drug Discov. 2007 Dec;6(12):991-1000
10. Clarke A, Kulesegaram R. Hepatitis C transmission, where are we now?. Int J STD AIDS 2006 Feb; 17(2): 74-80.
11. van Geldrop W J, Numans M E, Berg H F, van Putten A M, Bouma M. NHG-Standaard Virushepatitis en andere leveraandoeningen, second revision. Huisarts wet 2007:50(13):666-681.
12. Health Council of the Netherlands: Committee on Hepatitis C. Detection and treatment of people with hepatitis C. Rijswijk: Health Council of the Netherlands, 1997; publication no. 1997/19.
13. Richmond J A, Dunning T L, Desmond P V, Health Professionals' Attitudes Toward Caring for People With Hepatitis C. J Viral Hepat. 2007;14(9):624-632.
14. Nagykaldi Z, Mold J W, Aspy C B. Practice facilitators: a review of the literature. Fam Med. 2005 Sep;37(8):581-588.
15. Hermens R P, Hak E, Hulscher M E, Braspenning J C, Grol R P. Adherence to guidelines on cervical cancer screening in general practice: programme elements of successful implementation. Br J Gen Pract. 2001 Nov;51(472):897-903.
16. van Essen G A, Kuyvenhoven M M, de Melker R A. Implementing the Dutch College of General Practitioner's guidelines for influenza vaccination: an intervention study. Br J Gen Pract. 1997 Jan;47(414):25-29.
17. Nagykaldi Z, Mold J W, Robinson A, Niebauer L, Ford A. Practice facilitators and practice-based research networks. J Am Board Fam Med. 2006;19(5):506-510.
18. Thompson-Coon J., Castelnuovo E, Pitt M, Cramp M, Siebert U, Stein K. Case finding for hepatitis C in primary care: a cost utility analysis. Fam Pract 2006 August;23(4):393-406.
19. Stein K, Dalziel K, Walker A, Jenkins B, Round A, Royle P. Screening for Hepatitis C in injecting drug users: a cost utility analysis. J Public Health (Oxf) 2004 March;26(1):61-71.
20. Sroczynski G, Esteban E, Conrads-Frank A et al. Long-term effectiveness and cost-effectiveness of screening for hepatitis C virus infection. Eur J Public Health 2009 June;19(3):245-53.
21. Sahajian F, Excler G, Bailly F,et al. Hepatitis C screening practices among private practitioners: impact of an information campaign. Gastroenterol. Clin Biol. 2004 Aug-Sep;28(8-9):714-9.

22. Roudot-Thoraval F, Monnet E, et al. Strategies of hepatitis C screening in general practice. Results of a two-center randomized trial. Article in French [Stratégies de dépistage de l'hépatite virale C en Médecine générale]. Gastroenterol Clin Biol. 2000 Nov;24(11):1037-41.
23. Smith BJ, Bauman AE, Chen J, et al. Hepatitis C in Australia: impact of a mass media campaign. Am J Prev Med. 2006 Dec;31(6):492-8.
24. Chen J, Smith BJ, Loveday S, et al. Impact of a mass media campaign upon calls to the New South Wales Hep C helpline. Health Promot J Austr. 2005 Apr;16(1):11-4.

Chapter 2.2

Active case finding among drug users is essential for the identification of hepatitis C infection in addiction care

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Abstract

Introduction: Hepatitis C virus (HCV) infection is an increasingly recognized problem among hard drug users (HDU), because of its high prevalence and serious long term complications. However, mainly due the lack of clinical symptoms, HCV infected HDU are only incidentally diagnosed. Because treatment possibilities have improved substantially in the past decade, HCV infected HDU need to be identified in an early stage of disease. In this study we assessed the effectiveness of an active case finding strategy for HCV targeting HDU in addiction care.

Methods: In a non-randomized intervention study with pre-post comparison the effectiveness of 'active HCV case finding' among HDU with pro-active consultation and 'on the spot' diagnostic testing, was compared to recommended common practice which consists of passive distribution of information (brochures and posters) on HCV in addiction care centres. In an intervention and control region a standardized policy for common practice was implemented. In addition, all addiction care workers in the intervention region were instructed to pro-actively approach every attending HDU and offer HCV consultation and 'on the spot' anti-HCV testing. The number of consultations and (positive) anti-HCV tests performed was compared between the two regions and controlled for pre-intervention data.

Results: In the addiction care centres with 'active case finding' 213 consultations were registered during the registration period of which 191 (89.7%) concerned HDU. Anti-HCV tests were performed in 168 HDU of which 56 (33.3%) were positive. In the control region and the pre-intervention assessment no HCV consultations and no HCV testing took place.

Conclusion: An 'active case finding' strategy among hard drug users with pro-active consultation and facilitation of 'on the spot' testing substantially increases the number of identified HCV infected hard drug users, whereas common practice does not. Therefore, active HCV case finding should be implemented in routine addiction care practice.

Introduction

Infection with the hepatitis C virus (HCV) is considered a major health threat, affecting approximately 3% of the world's population and 0.2% of the Dutch population.[1-3] The strictly blood-bound infection pathway has led to the identification of several risk groups. Among injecting drug users (IDU), HCV prevalence is estimated at 60 to 80%.[4] In hard drug users (HDU) who do not use injecting techniques, reported HCV prevalence ranges from 2 to 35% (median 14%).[5] This makes HDU and specifically IDU by far the group most at risk of HCV infection and its long term complications. HCV infection leads to chronic hepatitis in 80% of cases. After 20 to 30 years 20% of the chronically infected patients will develop liver cirrhosis. Of these patients 1 to 4% develops hepatocellular cancer annually.[6,7] Since this process is accelerated by HIV and HBV co-infection and by alcohol use, prognosis of HCV infection among HDU is possibly even worse.[6]

In the past decade HCV treatment has improved considerably with regard to success rate and treatment duration. Today 40 to 50% of patients infected with genotype 1 and 4 and over 75% of patients with genotype 2 and 3 can be cured after treatment which usually lasts 24 to 48 weeks.[8] So far, only a minority of the people infected with HCV in the general population has been identified.[9] As nowadays most patients can be treated effectively, all HCV infected individuals need to be diagnosed.[10-12]

Given the atypical signs and symptoms, case finding of HCV infection is a challenge. First, the patient at risk has to be identified. Next, the necessity of undergoing diagnostic testing has to be discussed and finally, the person at risk has to actually be tested. In addiction care HCV case finding is even more challenging as it is focussed on drug substitution and direct health threats and takes place in a complex patient-doctor interaction.[13] In addition, the perception of HCV infection as relatively benign, the fear of investigations and treatment and the absence of clinical symptoms withhold HDU from seeking HCV care.[14] Therefore, a pro-active attitude by addiction care workers seems needed to improve case finding among HDU.[15]

Aims

We compared the effectiveness of active HCV case finding among HDU with pro-active consultation and 'on the spot' diagnostic testing to recommended common practice, consisting of passive distribution of information on HCV in addiction care.

Methods

Design
A non-randomized intervention with pre-post design was conducted, comparing the effectiveness of a structured 'active case finding' strategy to common practice in two regions with comparable populations of injecting and non-injecting HDU in the Netherlands.

The campaign took place between May 2007 and September 2008. In the Netherlands, addiction care centres provide structured care for HDU, including methadone dispensing programmes and health education in regional outpatient clinics. The addiction care centres where the intervention was implemented included these outpatient clinics and the regional shelters for the homeless. The 'active case finding' strategy was implemented in addiction care centres in the Rotterdam region (approximately 580,000 inhabitants) and compared to common practice in addiction care centres in the Dordrecht region (approximately 120,000 inhabitants).

Before the intervention period there was no standardized policy targeting HCV in addiction care, but passive distribution of information on HCV through brochures and posters was recommended. In all addiction care centres in the intervention and control region a standardized policy for this recommended common practice was implemented. Informative posters and brochures on HCV were on display and available in the addiction care centres and a training course on HCV infection, its risk groups and specific HCV consultation techniques was offered to addiction care workers (nurses and physicians).

'Active case finding'
In the 'active case finding' region all addiction care workers were instructed to pro-actively approach every HDU attending the addiction care centres during the intervention period and offer HCV consultation and 'on the spot' testing. In addition, informative group meetings were offered to HDU by the 'Mainline foundation for Health and prevention work for drug users' (Mainline).

Common practice
The recommended common practice was implemented in the control region. There were no informative group meetings for HDU and consultation and testing were only offered on request by an HDU.

Participants
Both the 'active case finding' intervention and the standardized policy for common

practice were implemented by the Netherlands Institute of Mental Health and Addiction (Trimbos), Mainline, and the Rotterdam Public Health Service (GGD). These HCV case finding strategies targeted injecting and non-injecting HDU attending the regional outpatient clinics for opiate substitution and shelters for the homeless.
In the 'active case finding' region, the intervention was implemented at seven locations. Two opiate substitution treatment clinics which are part of a mental health organisation specialized in addiction care (Bouman GGZ), two shelters run by the Salvation Army and three social service centres (CVD) for the homeless. These institutions provided shelter and/or care for approximately 750 clients of whom roughly 88% were HDU and 50% were IDU. In the control region one large opiate substitution treatment clinic participated, which is also part of the Bouman mental health organisation. This location provides care for approximately 250 clients of whom roughly 99% were HDU and 50% were IDU. Since the addiction care centres in the intervention and control region were part of the same organisation, they had a comparable organisational structure and routine addiction care practice.

Outcome assessment and data collection
Data on consultations and testing during the interventions was prospectively collected by addiction care professionals starting from the start of the campaign in May 2007 to June 2008. The primary outcome was the number of HCV consultations, anti-HCV tests performed and the resulting positive anti-HCV tests. Differences in outcome between intervention and control region were analysed and reported with 95% CI. To determine the number of HCV consultations and tests performed in previous years without the standardized HCV policy, a pre-intervention assessment was conducted by the 'Infectious Disease Control department' of the Rotterdam Public Health Service. Analyses were performed using Excel and R statistical package. Because of low numbers, 95% confidence intervals were determined based on proportion testing using the modified Wald method.

Results

In the 'active case finding' region 26 addiction care professionals participated in the training courses and 180 HDU attended the informative group meetings. In the control region three addiction care professionals participated in the training courses.

Hepatitis C related consultation and testing
In the 'active case finding' region 213 HCV consultations were registered (table 1). Of these, approximately 90% concerned HDU of whom less than half (44%) had a history

of injecting drug use. A total of 186 individuals were tested for anti-HCV. This includes 168 HDU (90% of total tests) of whom 56 (33%) were anti-HCV positive. 67 of the tested individuals were IDU, of whom 49 (73%) had a positive test. All but one of the positive tests concerned HDU of whom 88% had a history of IDU. Genotype one and four were present in more than half (59%) of the infected individuals, which is comparable to the genotype distribution among HDU in the Netherlands.[3]

In the control region 300 brochures on HCV were distributed. This did not result in any HCV consultation or testing. The pre-intervention assessment demonstrated that HCV consultation and testing were not systematically registered, but the scarce information available suggests that this rarely occurred. Therefore, the number of HCV tests performed in previous years was considered negligible.

Table 1: Hepatitis C related consultations and tests in intervention region, control region and pre-intervention assessment

	Absolute number (%, 95% CI)
'Active case finding' strategy	
Registered consultations – Total	213
Registered consultations – Hard drug users (% of total number of registered consultations, N = 213)	191 (89.7%; 95%CI 84.8-93.1%)
Registered consultations – Injecting drug users (% of total number of consulting HDU, N = 191)	84 (44.0%; 95%CI 37.1-51.1%)
Anti-HCV tests performed – Total (% of total number of registered consultations, N = 213)	186 (87.3%; 95%CI 82.1-91.2%)
Anti-HCV tests performed – Hard drug users (% of total number of HCV tests, N = 186)	168 (90.3%; 95%CI 85.2-93.9%
Anti-HCV tests performed – Injecting drug users (% of number of HCV tests in HDU, N = 168)	67 (39.9%; 95%CI 32.8-47.4%)
Positive anti-HCV tests – Total (% of total number of HCV tests, N = 186)	57 (30.6%; 95%CI 24.5-37.6%)
Positive anti-HCV tests – Hard drug users (% of total number of positive HCV tests, N = 57)	56 (98.2%; 95%CI 89.7-100%)
Positive anti-HCV tests – Injecting drug users (% IDU of total HDU tested positive, N = 56) (% IDU tested positive of total tested IDU, N = 67)	49 (87.5%; 95%CI 76.1-94.1%) (73.1%; 95%CI 61.4-82.4%)
Common practice	
Registered consultations and anti-HCV tests	None
Pre-intervention assessment	
Registered consultations and anti-HCV tests	None

Discussion

Summary of findings

The 'active case finding' strategy, actively offering consultation and 'on the spot' testing to all attending hard drug users in addiction care, substantially increased the number of HCV consultations and the number of HCV carriers found whereas common practice did not. This clearly demonstrates the need for an active policy for HCV case finding in addiction care.

We did not evaluate the different components of the intervention, so conclusions about the effective elements are somewhat speculative. However, we think that the fact that HCV is offered as part of the routine consultation and that test facilities are offered immediately on the spot are key to the success of the intervention. HDU are a difficult group for medical interventions, due to their generally impulsive lifestyle and short term focus. By confronting them with the need for HCV testing in routine consultation their attention is captured successfully. This is reflected in the high number of consultations, which is likely to be a direct consequence of a pro-active approach and the high test uptake after consultation, which can probably be attributed to the 'on the spot' testing facilities.

Limitations

The non-random design, the fact that the intervention and control region were not equal in size and the limited reliability of the pre-intervention data are the main limitations of the study. In addition, there is a slight chance of contamination between both strategies because the participating addiction care centres in the two regions partly belong to the same organisation and because there is a possibility of commuting HDU.

The larger intervention region with a higher number of participating addiction care centres could have resulted in an overestimation of the effect of the 'active case finding' strategy. However, this study demonstrates that in both the control region and in the pre-intervention period consultation and testing for HCV was rare, underlining that HCV consultation is not part of routine practice in addiction care. This finding, combined with the magnitude of the effect in the 'active case finding' region, provides a rather robust result and makes it unlikely that the demonstrated difference between the strategies can be explained by limitations of the design.

We only studied the effect of the intervention on HCV consultation and testing. The optimal assessment of effectiveness of a HCV case finding strategy focuses on the number of patients successfully treated. Complete evaluation of treatment success after diagnosis requires a longitudinal design with years of follow-up. With this purpose

individual treatment results continue to be monitored by the Rotterdam Public Health Service and the University Medical Centre Rotterdam and will be published in the future.[16]

Recent research has demonstrated that HCV can be treated successfully, even if the patient is an active drug user, alcohol dependant or has a psychiatric illness.[17-19] In addition, it has been demonstrated that those who have been treated successfully are at low risk of reinfection if adequate guidance is provided.[20] Therefore, initial case finding of HCV among HDU seems to be key to preventing its long term complications.

Considering the high prevalence of co-infection with hepatitis B virus (HBV) and Human Immunodeficiency Virus (HIV) in the HDU population and the need for improving screening of these diseases in drug users, it seems worthwhile to consider combined screening programmes for these diseases. Screening programmes for HBV and HIV are demonstrated to be effective in drug users.[21,22] Combining HIV and HBV with HCV in one screening campaign would reduce total campaign costs and increase effectiveness.

The success of the 'active case finding' strategy depends on the reduction of barriers which hamper compliance with the consultation and testing process among drug users. To achieve this, 'on the spot' testing and consultation facilities need to be established in every addiction care institute, in close collaboration with hospital gastroenterology departments. For structural implementation financial resources for HCV case finding programmes in addiction care centres should be made available.

Conclusion

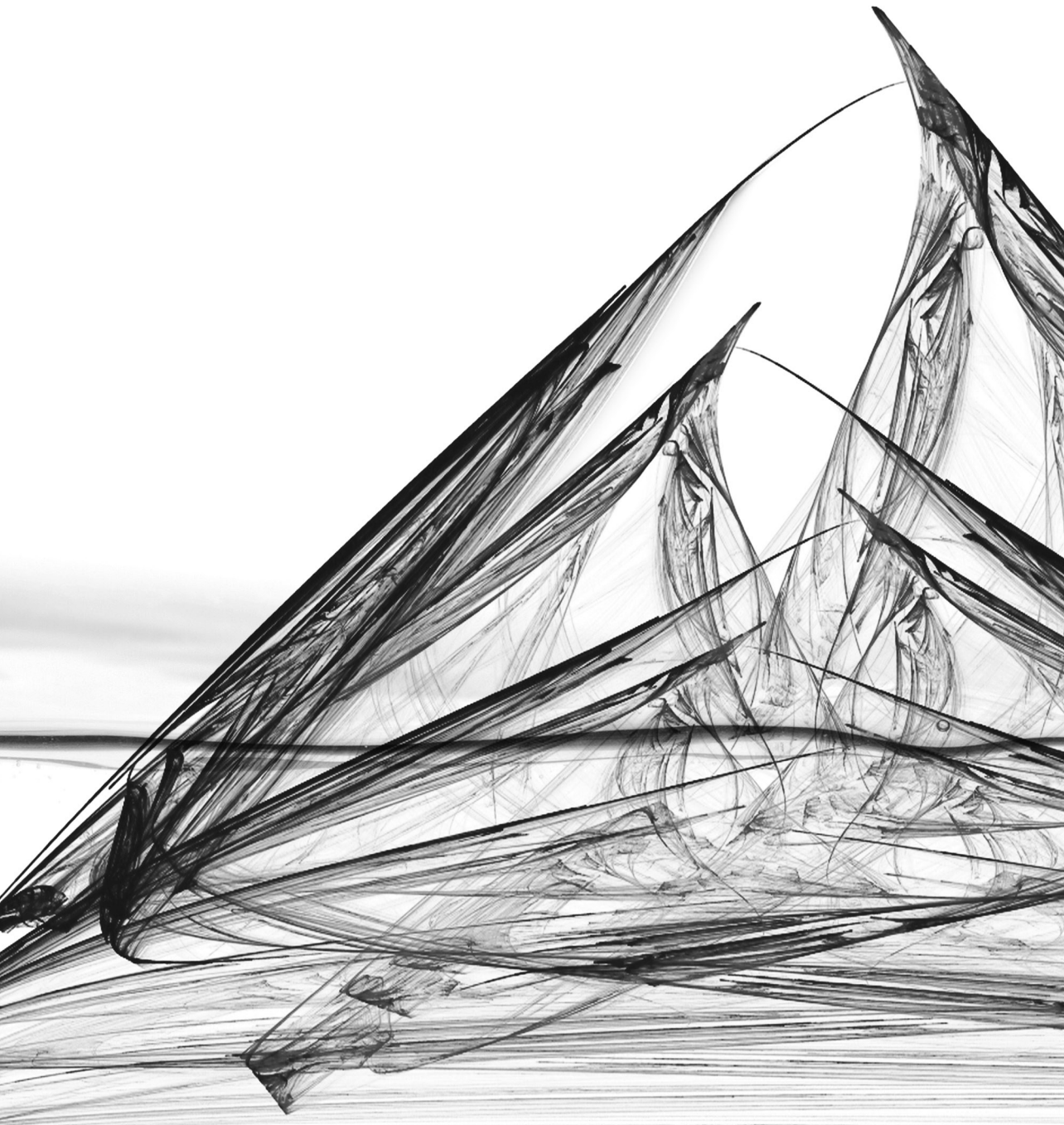
An 'active case finding' strategy, with actively offered consultation and facilitation of 'on the spot' testing in addiction care, effectively identifies HCV infected hard drug users whereas common practice does not. Therefore active HCV case finding should be implemented in routine addiction care practice.

Acknowledgements

We thank the 'Mainline foundation' and the Netherlands Institute for Health Promotion (NIGZ) for their role in the development and implementation of the hepatitis C campaign aimed at hard drug users. Funding for this study was provided by The Netherlands Organization for Health Research and Development (ZonMw).

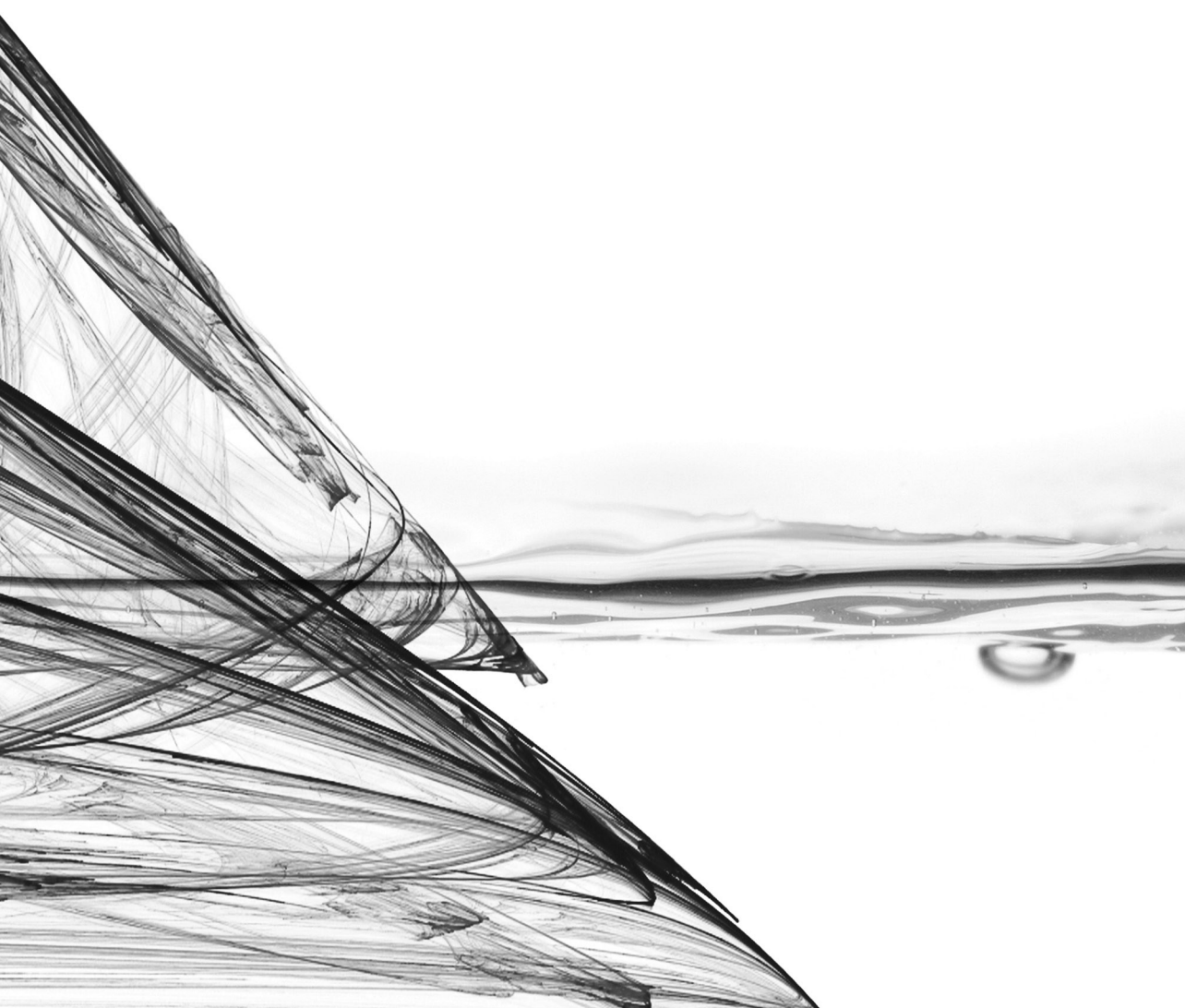
Reference List

1. Hepatitis C--global prevalence (update). Wkly Epidemiol Rec 1999; 74(49):425-427.
2. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis 2005; 5(9):558-567.
3. Slavenburg S, Verduyn-Lunel FM, Hermsen JT, Melchers WJ, te Morsche RH, Drenth JP. Prevalence of hepatitis C in the general population in the Netherlands. Neth J Med 2008; 66(1):13-17.
4. Nelson PK, Mathers BM, Cowie B, Hagan H, Des JD, Horyniak D et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. Lancet 2011.
5. Scheinmann R, Hagan H, Lelutiu-Weinberger C, Stern R, Des J, Flom PL et al. Non-injection drug use and Hepatitis C Virus: a systematic review. Drug Alcohol Depend 2007; 89(1):1-12.
6. Seeff LB. Natural history of chronic hepatitis C. Hepatology 2002; 36(5 Suppl 1):S35-S46.
7. Lauer GM, Walker BD. Hepatitis C virus infection. N Engl J Med 2001; 345(1):41-52.
8. Manns MP, Foster GR, Rockstroh JK, Zeuzem S, Zoulim F, Houghton M. The way forward in HCV treatment--finding the right path. Nat Rev Drug Discov 2007; 6(12):991-1000.
9. Cornberg M, Razavi HA, Alberti A, Bernasconi E, Buti M, Cooper C et al. A systematic review of hepatitis C virus epidemiology in Europe, Canada and Israel. Liver Int 2011; 31 Suppl 2:30-60.
10. Health Council of the Netherlands: Committee on hepatitis C. Detection and treatment of people with hepatitis C. 1997/19. 1997. Rijswijk.
11. Kok A, Zuure FR, Weegink CJ, Coutinho RA, Prins M. [Hepatitis C in the Netherlands: sparse data on the current prevalence and the necessity for epidemiological studies and innovative methods for detecting infected individuals]. Ned Tijdschr Geneeskd 2007; 151(43):2367-2371.
12. Gravitz L. a smouldering public-health crisis. Nature 2011; 474(7350):S2-S4.
13. Flanagan SM, Hancock B. 'Reaching the hard to reach'--lessons learned from the VCS (voluntary and community Sector). A qualitative study. BMC Health Serv Res 2010; 10:92.
14. Swan D, Long J, Carr O, Flanagan J, Irish H, Keating S et al. Barriers to and facilitators of hepatitis C testing, management, and treatment among current and former injecting drug users: a qualitative exploration. AIDS Patient Care STDS 2010; 24(12):753-762.
15. Camoni L, Federico B, Capelli G, Salfa MC, Regine V, Nicoletti G et al. [Proportion of drug users in treatment who have never undergone serological testing for HIV, HBV and HCV and correlates of failure to undergo testing: Italy, 2005-2007]. Ann Ig 2009; 21(4):315-327.
16. Breemer JN, de Jong W.M., Krummacher N., Wolter R. Evaluatierapport Pilotproject Actief Testen in de GGZ en Maatschappelijke opvang 2007-2008. GGD Rotterdam-Rijnmond, editor. 2009.
17. Lindenburg CE, Lambers FA, Urbanus AT, Schinkel J, Jansen PL, Krol A et al. Hepatitis C testing and treatment among active drug users in Amsterdam: results from the DUTCH-C project. Eur J Gastroenterol Hepatol 2010.
18. Hellard M, Sacks-Davis R, Gold J. Hepatitis C treatment for injection drug users: a review of the available evidence. Clin Infect Dis 2009; 49(4):561-573.
19. Grebely J, Matthews GV, Hellard M, Shaw D, van B, I, Petoumenos K et al. Adherence to treatment for recently acquired hepatitis C virus (HCV) infection among injecting drug users. J Hepatol 2011; 55(1):76-85.
20. Grebely J, Knight E, Ngai T, Genoway KA, Raffa JD, Storms M et al. Reinfection with hepatitis C virus following sustained virological response in injection drug users. J Gastroenterol Hepatol 2010; 25(7):1281-1284.
21. Farrell M, Battersby M, Strang J. Screening for hepatitis B and vaccination of injecting drug users in NHS drug treatment services. Br J Addict 1990; 85(12):1657-1659.
22. Des Jarlais DC, Arasteh K, Gwadz M. Increasing HIV prevention and care for injecting drug users. Lancet 2010; 375(9719):961-963.



Chapter 3

Economic considerations



Chapter 3.1

Cost-effectiveness of targeted screening for hepatitis C in the Netherlands

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Epidemiology and Infection 2011 Feb; 16:1-12.

Abstract

Introduction: On account of the serious complications of hepatitis C virus (HCV) infection and the improved treatment possibilities, the need to improve HCV awareness and case-finding is increasingly recognized.

Methods: To optimize a future national campaign with this objective, three pilot campaigns were executed in three regions in The Netherlands. One campaign was aimed at the general population, a second (similar) campaign was extended with a support programme for primary care and a third campaign was specifically aimed at hard drug users. Data from the pilot campaigns were used to build a mathematical model to estimate the incremental cost-effectiveness ratio of the different campaigns.

Results: The HCV campaign aimed at the general public without support for primary care did not improve case finding. The ICER of implementing a countrywide HCV campaign aimed the general public with complementary support for primary care is estimated at €11,297 per QALY. The ICER of implementing a national HCV campaign aimed at hard drug users is estimated at €7,321 per QALY.

Conclusion: Considering a Dutch cut-off point of €20,000 as a favourable cost-effectiveness ratio, both the HCV campaign aimed at hard drug users as well as the HCV campaign aimed at the general public with complementary support for primary care, are to be considered cost-effective strategies to improve case finding and prevent future complications of HCV. Since the HCV campaign without primary care practice support did not result in improved case finding, a support programme for primary care practices is vital in achieving cost-effectiveness for a HCV campaign aimed at the general public.

Introduction

Infection with hepatitis C virus (HCV) is increasingly being recognized as a serious health threat in today's society, but still remains relatively unknown in the general population and general practitioners (GPs) in low endemic countries. It is estimated that 2–3% of the world's population (123–170 million people) are infected with HCV, of which a large proportion remains undiagnosed.[1,2] HCV infection may have serious long-term complications. After about 25 years, 20–30% of the chronic carriers have developed liver cirrhosis and of these patients 1–4% develop a hepatocellular carcinoma each year. Fortunately, treatment possibilities have improved dramatically over the past decade, to a point were up to 51% of HCV-infected patients with genotypes 1 or 4 and up to 90% of HCV-infected patients with genotypes 2 or 3 can be cured after 24–48 weeks of antiviral treatment.[3–6] In The Netherlands, the prevalence of HCV is estimated to be between 0.1% and 0.4%.[7,8] Because of the lack of clinical symptoms and despite the serious consequences of HCV infection, it is estimated that only one quarter of the carriers in The Netherlands have been diagnosed.[8–10] Since the virus is transmitted by blood–blood contact, several high-risk groups can be identified. A recent study in The Netherlands shows that 45% of the identified carriers were injecting drug users (IDU) and 41% were people with a country of origin other than The Netherlands.[11] Among IDU in The Netherlands, a HCV prevalence of 47–79% has been found.[9] In immigrants, the prevalence varies up to 21.9% in Egyptian immigrants but is generally much lower than in IDU.[12] The prevalence in other risk groups, such as certain travellers and recipients of blood products, differs depending on the circumstances of the exposure but is generally lower than in IDU and high-risk immigrants.

In 1997 the Dutch Health Council stated that a campaign was necessary in order to increase public awareness of HCV.[10] In 2007, three pilot campaigns were constructed to prepare for and to optimize the effectiveness of a future national campaign:

1. the 'general campaign' - to reach the general population;
2. the 'support campaign' - to reach the general population, extended with a support programme for primary care;
3. the 'drug users campaign' - specifically aimed at present or former hard-drug users (HDU).

The incremental cost-effectiveness ratio (ICER) can be used to support the decision whether or not to implement newly developed healthcare interventions. The ICER is the ratio of the additional effects (e.g. life-years gained) of an intervention to its additional costs.[13] This number can for instance be used as an objective measure to compare cost-effectiveness of different strategies for case finding. The aim of this study is to estimate

the ICERs of implementing each of the three campaigns nationwide in The Netherlands compared to 'current practice '. Current practice was defined as usual care and attention as deemed appropriate by the GP consulted, regarding any consultations concerning HCV.

Methods

Description of the pilot campaigns

The general campaign and the support campaign were implemented from October 2007 to January 2008, in two similar regions in the centre of The Netherlands (the Gelre-IJssel region and the Eemland region). These regions have a population structure that is representative of The Netherlands regarding age and the presence of individuals and groups with an increased risk of HCV infection (immigrants and known HDU).[14]

General campaign

The general campaign consisted of local broadcasting of radio advertisements, publishing advertisements in newspapers and the distribution of specially designed posters and brochures in public areas where risk groups were expected to congregate. In the Gelre-IJssel region, this campaign was implemented without any support for primary care.

Support campaign

A support programme especially designed for primary care was implemented in the Eemland region, complementary to a general campaign identical to the campaign implemented in the Gelre-IJssel region. This support programme consisted of (voluntary) plenary courses for GPs and the employment of two practice facilitators who visited the GP practices on appointment to provide information regarding HCV and the campaign.

Drug users campaign

The drug users campaign was implemented from May 2007 to September 2008 and was aimed at increasing the knowledge of HCV in HDU, in particular IDU, and increasing the willingness of these individuals to cooperate in HCV testing. This campaign was implemented in Rotterdam, which is the second largest city in the country with about 600,000 inhabitants. Based on data from the National Drug Monitor, it can be accurately estimated that Rotterdam has 5,000 HDU, which is 15% of all HDU in The Netherlands.[15] In Rotterdam, 26 addiction care professionals were trained to provide HCV counselling, which was systematically and actively offered to HDU at their meeting venues. In addition, three informative meetings were organized which were attended by 180 HDU. At the counselling sessions and meetings, information was provided about HCV

infection and HDU were motivated and facilitated to be tested for HCV infection.[16]

Costs and effects of nationwide campaigns

The total number of anti-HCV tests performed and the proportion of HCV-positive test results were measured in all laboratories in the pilot regions of the general and support campaigns. These data were compared to a similar period of 4 months in previous years (October 2007 to January 2008 vs. October to January in the two previous years).

For the drug users campaign, data regarding the number of hepatitis C tests were registered by the addiction care centres which provided counselling and testing facilities in Rotterdam and the Municipal Health Service (GGD) Rotterdam – Rijnmond.[14,16]

Pre-intervention assessments showed that HCV testing in addiction care took place exclusively when specifically requested by HDU. Data assessment by the Infectious Disease Control Department of the Municipal Health Service Organization of Rotterdam showed that this had happened sporadically and was inadequately registered. The number of tests in previous years was therefore considered negligible.[16]

Cost estimates of implementing the campaigns nationwide were based on extrapolation of the costs of the pilot projects. The organizations involved in the three different pilot campaigns provided a detailed, standardized overview containing information regarding time investment by specified professionals for organization, training and other activities and direct costs of materials, design and other expenses. These organizations were The Netherlands Institute for Health Promotion and Disease Prevention (NIGZ) (general campaign), the Julius Center for Health Sciences and Primary Care (support campaign), the Trimbos institute, Netherlands Institute of Mental Health and Addiction and the Mainline Foundation (drug users campaign). The results of the pilot campaigns, in terms of additional number of tests performed and HCV carriers identified, were used to compute the number of additional HCV carriers that would be expected to be found if the campaigns were implemented nationwide. For the general campaign and the support campaign, we used the number of inhabitants in the regions where the campaigns were performed relative to the total number of inhabitants of The Netherlands (data provided by Statistics Netherlands). For the drug users campaign, we used the estimated numbers of HDU in Rotterdam relative to overall hard drug use in The Netherlands.[15]

The health economic model

After calculating the expected number of additional HCV carriers identified through a campaign, the costs and effects of finding one carrier were estimated. The effect of a healthcare intervention was measured in quality adjusted life years (QALYs) gained. QALYs are calculated as the product of life years experienced after an intervention (here HCV case finding) and the quality of life of the patient during those years, expressed as a figure between 0 (death) and 1 (normal quality of life). To compute the expected savings in costs and gain in QALYs as a result of detecting one HCV carrier, we use a modified version of a previously published Markov model.[17] This model was adapted to fit the current Dutch situation. It describes the history of a chronic HCV infection considering the dependence on age at time of testing. It consists of nine health states for each of which mortality rates, healthcare costs and quality of life are estimated. Transition probabilities indicate the annual probability of moving from one state to another. A HCV carrier who is tested positively has a treatment probability that depends on the person's health state. Survival rates of the general Dutch population were obtained from Statistics Netherlands.[18] HDU are assumed to have a 15-year shorter life expectancy.[19] A lifelong time horizon was used. The costs of each of the nine different health states were estimated in the original model, and converted to 2007 Euros using consumer price indices as provided by OECD.[20] The analysis was performed from a healthcare perspective, which means that only direct medical costs are included. Costs of consultations, tests and treatment are shown in Table 1.

Treatment costs were corrected for discontinuation of treatment as observed in the paper by Veldt et al. and were updated for the current standard of treatment (peg-interferon vs. interferon).[22] In accordance with Dutch pharmaco-economic guidelines, future (avoided) healthcare costs were discounted at 4% and health outcomes (QALYs) were discounted at 1.5%.[23]

For each campaign type, two versions of the Markov model were employed simultaneously to compare the situation with and without the campaign. The two Markov models were run for each age group of 1 year, for ages 0–102 years. The total QALYs gained and treatment costs are the sum of these outcomes for each age, weighted according to the age distribution of the carriers.

Presumed clinical course of HCV identification and treatment

Based on Dutch HCV prevalence and infectious diseases monitoring data of the National Institute for Public Health and the Environment, we estimated the annual probability of identification of a chronic HCV carrier without intervention to be 1.2%.[7, 8, 24]

The course after identification specified for members of the general population and for HDU is depicted in Figure 1.

Table 1. Costs of diagnostic and therapeutic process

Diagnostic tests and consultations before treatment	Costs in €
First consultation GP to determine need for anti-HCV testing *	9.00
First counselling hard drug user to determine need for anti-HCV testing[21]	21.17
immunoassay (EIA) screening tests + fee †	25.30
Polymerase Chain Reaction (PCR) + fee †	120.10
Second consultation GP in case of positive test *	9.00
Second consultation GP (telephone) in case of negative test *	3.95
Second counselling hard drug user positive test[21]	28.23
Second counselling hard drug user negative test[21]	7.06
Total cost of medication and diagnostic procedures during treatment per patient after correcting for early discontinuation of treatment[22,26] ‡	**Costs in €**
Genotype 1 and 4 (48 weeks)	15,772
Genotype 2 and 3 (24 weeks)	9,582

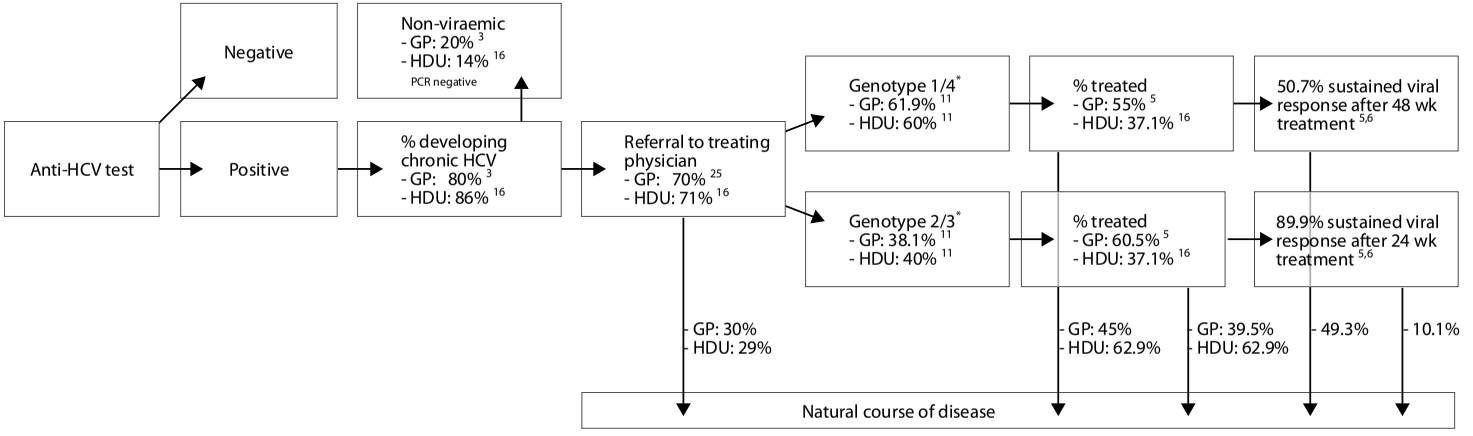
** Julius Center for Health Sciences and Primary Care, † Laboratory MMC Amersfoort, ‡ Costs are adjusted for the current standard treatment (peg-interferon alfa and ribavirin) and include diagnostic monitoring, occurrence of side effects and early discontinuation of treatment*

The diagnostic process in The Netherlands starts with a HCV-antibody test based on the use of enzyme immunoassays (EIA). A positive anti-HCV test indicates that the patient has been infected in the past. Of the anti-HCV positive patients, an estimated 80–86% fails to clear the virus and are considered chronic carriers.[3,16] To determine if the patient has become a chronic HCV carrier, a polymerase chain reaction (PCR) is performed. If the PCR is positive the patient should be referred to a specialist.

A recent study on referral of HCV-positive patients showed that referral by untrained GPs occurs in 50% of HCV-positive cases.[25] Since the GP support programme encourages GPs to refer HCV-positive patients, an increase in referrals can be expected in the intervention region. Based on a study on referral and the underlying reasons for non-referral by de Jong et al., it can be assumed that referral during a campaign including a support programme for primary care will improve up to about 70%.[25] Follow-up of the pilot campaign aimed at HDU demonstrated that the referral rate in HDU is 71% after instruction of healthcare professionals.[16]

After referral, the genotype of the HCV is determined by a HCV genotype assay (LiPa). In the general public, 55% of carriers of genotypes 1 or 4 are treated for 48 weeks with a combination therapy consisting of a weekly dose of an average of 180-µg

Figure 1. Course of events after the first anti-HCV test and progression to possible outcomes .[3,5,6,11,16,25]



GP: General population. HDU: Hard Drug Users

** There is a very low percentage of genotype six in the Netherlands (1,7%). Due to a lack of information on treatment and natural course, our analysis is based on the assumption that only genotypes 1,2,3 and 4 are present in the Dutch population.*

peg-interferon-alfa and 1000–1200 mg ribavirin each day.[5,22,26] Of the patients infected with HCV genotypes 2 or 3, 60.5% are treated with the same therapy for 24 weeks.[5]
Among HDU, 37% of PCR-positive patients are treated (no distinction between genotypes available).[16] Prognosis depends on the health state of the patient at time of testing, patient age and response to treatment.[5,17] Model parameters are shown in Table 2. Those testing positive but not referred to treating physicians and those not treated after identification as a chronic carrier follow the natural history of HCV infection (see Fig. 1).

Sensitivity and scenario analyses

Multivariate sensitivity analyses were performed to discover which input parameters are most influential on the uncertainty in the ICERs. In a multivariate sensitivity analysis, next to uncertainty in the outcome due to individual model parameters, the impact of potential interactions between model parameters was also accounted for. Various values for model parameters were sampled in accordance with their likelihood of occurring. Details on the distribution functions used in the simulation can be found in the Supplementary material (available at the end of this chapter). The multivariate parameter sensitivity is expressed in terms of standardized regression coefficients (SRCs). Furthermore, parameter uncertainty was dealt with by probabilistic sensitivity analysis (PSA). Monte Carlo simulations were run until convergence of the results was obtained. This was achieved after 1,500 iterations for the support campaign and 1,000 iterations for the drug users campaign. For all input variables with uncertain values, a random value was drawn from the distribution given in the tables in the Supplementary material. Simulated net costs are plotted against the effects (QALYs) (Fig. 2). In addition, a cost-effectiveness acceptability curve was constructed, which shows the likelihood that hepatitis C campaigns are cost-effective for a range of cost-effectiveness thresholds (Fig. 3).
To illuminate the influence of the prevalence of HCV on the cost-effectiveness of the campaigns, a scenario analysis was performed. The HCV prevalence in urban regions was estimated to be approximately twice as high as in the rural campaign regions. The prevalence in the least densely populated regions of The Netherlands was estimated to be half the prevalence compared to the campaign region. This is based on estimations of the presence of risk groups, made by Statistics Netherlands and the National Drug Monitor.[15,27] Therefore the ICER of the support campaign and the drug users campaign was calculated for a region with double and half the prevalence. This implies that twice or half the number of HCV carriers will be identified.

Table 2. Clinical characteristics

Parameter	Value
General population	
Natural course - probability of chronic HCV infection[3]	80%
Percentage infections of genotype 1 or 4[11]	61.9%
Percentage infections of genotype 2 or 3[11]	38.1%
Referral rate[25]	70%
Percentage eligible and accepting treatment, genotype 1 or 4[5]	55%
Percentage eligible and accepting treatment, genotype 2 or 3[5]	60.5%
Percentage of eligible patients starting treatment in first year *	78%
Percentage of eligible patients starting treatment in second year *	20%
Hard drug users	
Probability of spontaneous clearance of virus[16]	14%
Percentage infections of genotype 1 or 4[11]	60.0%
Percentage infections of genotype 2 or 3[11]	40.0%
Referral rate[16]	71.43%
Percentage eligible and accepting treatment[16]	37.14%
Equal for general population and hard drug users	
Annual probability of identification in case of no campaign †	1.2%
Average age at testing, for drug users and the general population[11]	44.3
Probability of successful treatment, genotype 1 or 4, mild or moderate hepatitis[5]	54%
Probability of successful treatment, genotype 1 or 4, cirrhosis[5]	24%
Probability of successful treatment, genotype 2 or 3, mild or moderate hepatitis[5]	94%
Probability of successful treatment, genotype 2 or 3, cirrhosis[5]	48%
Percentage of HCV carriers with mild hepatitis at time of testing[6]	46%
Percentage of HCV carriers with moderate hepatitis at time of testing[6]	43%
Percentage of HCV carriers with cirrhosis at time of testing[6]	11%

** Derived from database infectious diseases University Medical Center Utrecht, † Estimation based on Dutch prevalence and monitoring data.[7,8,24]*

Results

Effects and costs of the general campaign

The results of the campaigns are summarized in Table 3. During the 4 months of the general campaign, the number of anti-HCV tests performed increased by 32, compared to the same period in the previous year (from 86 to 118 tests). None of these tests identified a HCV carrier, so there was no positive effect on case finding and no measurable effect of this campaign.[14] If implemented nationwide, the general campaign would cost about €490,000, plus €120,000 for the resulting consultations and anti-HCV tests.

Effects and costs of the support campaign

During the 4 months of the support campaign the number of anti-HCV tests performed increased by 115 (from 57 to 172 tests), resulting in the identification of three anti-HCV-positive patients (from 0 to 3 positive patients).[14] Since 80% of the infections are expected to lead to chronic disease, the expected number of patients with a positive PCR test is 0.8*3=2.4. Extrapolation of these results to a nationwide campaign leads to an estimated increase in the number of anti-HCV tests performed of 6,990 tests, leading to the identification of an additional 146 chronic HCV carriers. The costs for the nationwide support campaign are about €490,000 for the general campaign (as described above), €770,000 for the GP support programme and €1.2 million for the nationwide additional GP consultations, the requested tests and additional HCV treatments. This leads to a total cost of about €2.5 million (95% CI €1,715,139–3,820,432). Combining these numbers yields that the costs of the support campaign, including the additional testing and treatment, amount to €17,000 (95% CI €10,655–57,364) for each additionally identified chronic HCV carrier (Table 4).

Effects and costs of the drug users campaign

During the drug users campaign 213 counselling sessions took place. This led to 186 additional anti-HCV tests, resulting in the identification of 57 anti-HCV positive patients of whom 49 had a positive PCR test (and can therefore be considered chronic HCV patients).[16] Evaluation by the Infectious Disease Control Department of the Municipal Health Service of Rotterdam showed that hepatitis C testing in a regular addiction-care setting only occurred sporadically over the past years.[16] Therefore, this cost-effectiveness analysis is based on the assumption that all the anti-HCV tests performed on HDU during the four campaign months were a direct consequence of the campaign. Extrapolating these data, it was estimated that nationwide implementation of the drug users campaign would result in the counselling of 1,427 additional persons, leading to 1,246 additional anti-HCV tests and the identification of 328 chronic carriers of HCV

(PCR confirmed). The additional costs of this implementation are about €156,000 for the campaign and €2 million for the resulting consultations, tests and treatments. This leads to a total cost of about €2.2 million (Table 4; 95% CI €1,599,613–2,880,541). Combining these numbers yields that the costs of the drug users campaign, including the resulting testing and treatment, amount to €6,700 (95% CI €5,422–8,170) for each chronic HCV carrier additionally identified.

Table 3. Extrapolation of regional results to national campaigns

Campaigns aimed at the general public		
Inhabitants of the Eemland region ('support campaign') *		269,125
Inhabitants of the Gelre IJssel region ('general campaign') †		166,315
Inhabitants of the Netherlands – 2007 ‡		16,357,992
	Regional campaign	Countrywide extrapolation
Additional number of persons tested for HCV[14] - 'general campaign'	32 (from 86 to 118)	3,147
Additional number of identified HCV carriers[14] - 'general campaign'	0	0
Additional number of persons tested for HCV[14] - 'support campaign'	115 (from 57 to 172)	6,990
Additional number of identified HCV carriers[14] - 'support campaign'	2.4 (from 0 to 2.4)	146
Campaign aimed at hard drug users		
Hard drug users in Rotterdam[15]		5,000
Hard drug users in the Netherlands[15]		33,500
	Regional campaign	Countrywide extrapolation
Additional number of hard drug users tested for anti-HCV[16]	186	1,246
Additional number of identified HCV carriers (PCR confirmed)[16]	49	328

** Official website of the Eemland region, † Official website of the Gelre IJssel region, ‡ Statistics Netherlands (CBS)*

Table 4. Costs of countrywide campaigns

Campaign	Costs in € (95% Confidence interval)
General campaign *	
Campaign organisation and execution	110,000
Campaign materials (radio ads, newspaper ads, posters, brochures, website, mailing costs)	380,000
Additional GP consultations and testing	120,373
(3147 tested persons of which 0 are chronic HCV carriers)	
Total costs of a 4 month national campaign	*610,373*
Campaign including support programme	
Campaign costs (organisation, execution and materials)	490,000
Plenary courses (30 min) provided for GPs (41 per meeting) †	160,508
Courses (45 min) for GPs in small setting (7 per meeting) †	469,557
Educational brochure for GPs and associates ‡	31,000
Support for general practice associates / assistants ¶	100,000
Other costs (mailings, personal communication) †	10,405
Additional GP consultations, testing and treatment resulting from campaign	1,206,545
(6990 tested persons of which 146 are chronic HCV carriers)	
Total costs of a 4 month national campaign. Including support for primary care practice and the resulting additional consultation, testing and treatment	*2,468,015 (1,715,139 - 3,820,432)*
Drug users campaign Ω	
Training and research	83,600
Project organisation	5,600
Project execution	45,000
Expenses (materials / travelling)	22,243
Additional consultations, testing and treatment	2,053,234
(1,246 tested persons of which 328 are chronic HCV carriers)	
Total costs of a national campaign, including consultations, testing and treatment	*2,209,677 (1,599,613-2,880,541)*

** the Netherlands Institute for Health Promotion and Disease Prevention (NIGZ), † Julius Center for Health Sciences and Primary Care, ‡ Dutch College of General Practitioners (NHG), ¶ Raedelijn, Ω the National Institute of Mental Health and Addiction in the Netherlands (Trimbos institute) and the Mainline foundation*

Model outcomes on cost-effectiveness

For the support campaign the discounted incremental cost per tested person is €353 (95% CI €245–547) with an associated gain of 0.031 QALYs (approximately 11 days, 95% CI 0.006–0.077). The resulting ICER is €11,297 (95% CI €6,804–38,685) per QALY. For the drug users campaign the discounted incremental cost per tested person is €1,773 (95% CI €1,284–2,311) with an associated gain of 0.242 QALYs (approximately 88 days, 95% CI 0.152–0.353). The resulting ICER is €7,321 per QALY (95% CI €5,214–10,436).

Sensitivity and scenario analysis

In the multivariate analysis, SRCs were determined. The SRCs indicate that the uncertainty of the ICER for the support campaign is primarily determined by uncertainty with regard to the number of cases found in the campaign (SRC=-0.64) and the referral rate (SRC=-0.15). Due to the nonlinearity of the ICER for the support campaign, the variance explained (R^2) by the linear regression model is only 0.42. When rank regression was performed instead, the same significant parameters were found (with an R^2 of 0.98) with SRCs of -0.94 and -0.21, respectively.

The sensitivity of the ICER for the drug users campaign was primarily determined by the age at testing (SRC=0.64). Furthermore, various costs and disease progression parameters play a role. There are about 10 such parameters with SRCs between 0.10 and 0.30. The variance explained (R^2) by the linear regression model that was fitted for this sensitivity analysis was 0.96. Details on the 10 most influential parameters for each campaign can be found in the Supplementary material (Table 4).

The uncertainty analysis indicates that the probability that the ICER for the support campaign remains below a threshold of €30,000 per QALY is over 95%. A threshold of €20,000 is often used in The Netherlands. The probability of an ICER below this threshold is 84%. For the drug users campaign the likelihood that the Dutch threshold value for an ICER will be exceeded is negligible. This is illustrated in the cost-effectiveness plane (Fig. 2) and, more specific, in the cost-effectiveness acceptability curve (Fig. 3).

The scenario analysis for double prevalence rates leads to an ICER of €7,099 in the support campaign and €6,676 in the drug users campaign. The scenario for half the prevalence rates yields ICERs of €15,760 and €7,056, respectively.

Figure 2. Cost-effectiveness plane

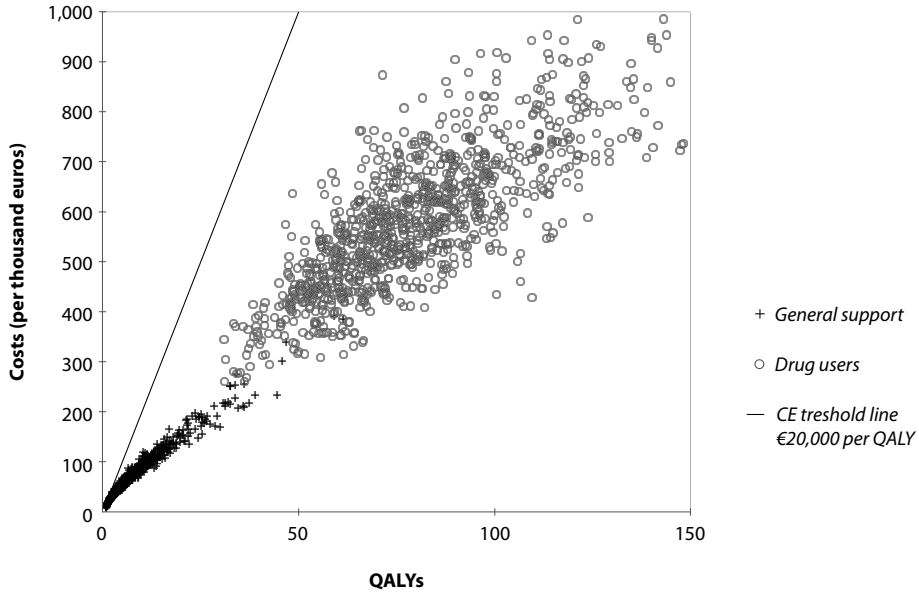
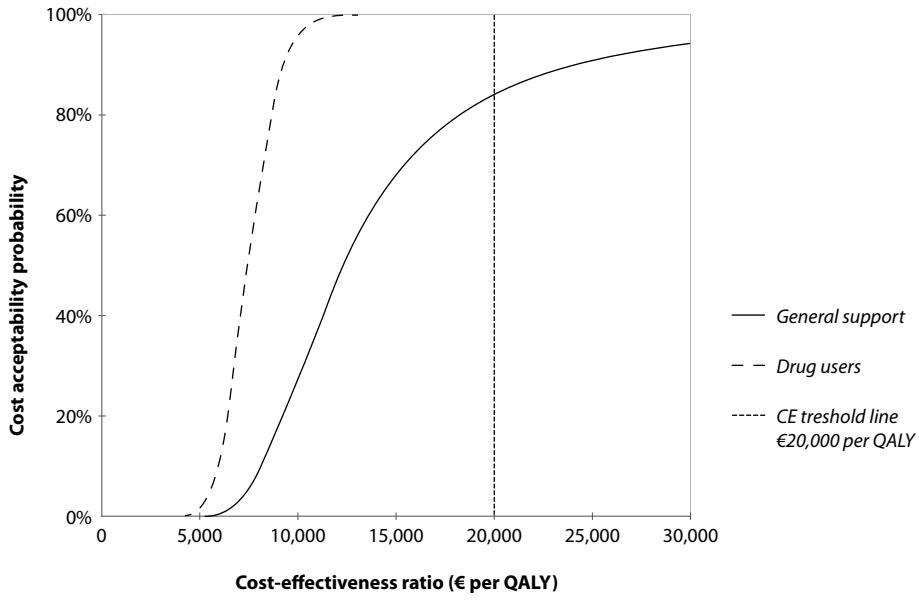


Figure 3. Acceptability curve



Discussion

Summary of findings

The cost-effectiveness of three different hepatitis C identification strategies was evaluated in order to optimize a future national hepatitis C campaign. Two similar campaigns (the general campaign and the support campaign) were aimed at risk groups in the general public, but only the support campaign implemented a complementary support programme for primary care. The third strategy entailed an active and 'on-the-spot' approach for HDU, facilitating the entire process from counselling to referral.

The general campaign did not result in an increase in the identification of HCV carriers which means there was no gain in effects and therefore no ICER could be calculated. Consequently this strategy is not cost-effective. In The Netherlands, an informal threshold for cost-effectiveness often quoted is €20,000 per QALY.[28] Considering this cut-off point, the ICERs of the support campaign and the drug users campaign indicate that both these campaign strategies should be considered cost-effective.

The ICER for the drug users campaign is hardly influenced by prevalence, as was shown in the sensitivity analysis. The reason for this is that 87% of the costs for each additionally identified HCV carrier in this campaign consists of treatment costs. In the support campaign treatment costs are 38% of the total costs for each additionally identified HCV case. Here the cost-effectiveness outcome is clearly determined by HCV prevalence.

Strengths and limitations

One of the main strengths of our study is that it is based on actual experience in performing HCV campaigns instead of hypothetical campaigns based on assumptions. Since the support campaign resulted in a low number of additionally identified HCV carriers, the generalizability of the ICER for this campaign is moderate at present and leaves room for research on a larger scale.

Even though the drug users campaign leads to a relatively large increase in the number of identified chronic HCV carriers, the resulting ICER is close to the ICER resulting from the support campaign. This can be explained by the lower effects in terms of QALYs gained, due to the reduced life expectancy of HDU which is estimated to be 15 years fewer than that of the general population.[19] We were not able to explicitly take into account the relatively high prevalence of HIV in HDU due to lack of information. The implementation of these effects in the model is expected to negatively influence the cost-effectiveness of the drug users campaign due to its negative effects on the prognosis and treatment of HCV.

The estimated discontinuation rate is based on a treatment with ribavarin and interferon.[22] In the current standard treatment, interferon has been replaced by

peg-interferon. Assuming that the current treatment is less burdensome, this might lead to an overestimation of treatment discontinuation and an underestimation of the success rate. Therefore the true cost-effectiveness may be more favourable than reflected in the estimated ICER.

An evaluation of a sustained effect after the campaign was not included in our calculations because these data were unavailable. Including these data could lead to a less favourable ICER if the increase in HCV-related tests and consultations persisted without increasing the number of HCV identifications. However, considering the results of the pilot campaigns, it is more likely that the increased awareness of GPs induced by the HCV campaign would lead to a higher number of identified HCV carriers at relatively low costs and consequently to a more favourable ICER.

This is the first paper on the cost-effectiveness of HCV campaigns in The Netherlands. Literature from other European countries is scarce, but it generally concludes that HCV campaigns are a moderately cost-effective means of identifying HCV carriers if aimed at high-risk groups in the general population. Thompson Coon et al. estimated the ICER at €20,000–24,000 per QALY, for both a non-targeted case finding strategy and for a targeted strategy (aimed at former IDU) in primary care within the UK.[5] Castelnuovo et al. and Stein et al. estimated the ICER of case finding in IDU in the UK at €20,000–23,000 per QALY if peg-interferon is used as standard therapy.[29,30]
Our data show a somewhat more favourable estimation of cost-effectiveness than existing studies.[31] The more favourable ICER found in our study can be explained by the fact that we evaluated a relatively cheap campaign with relatively large gains in QALYs per patient identified. The latter may be related to the fact that our analyses are based on treatment with peg-interferon and ribavirin which is less burdensome and more effective than less advanced forms of treatment used in other studies.[31]

Sensitivity analysis shows that the number of cases found have substantial influence on the cost-effectiveness of a campaign aimed at the general public. The prevalence of HCV is strongly correlated with the presence of risk groups (mainly immigrants and HDU), resulting in substantial regional differences. Consequently, in order to optimize cost-effectiveness, future HCV case finding campaigns should be focused on regions were a high concentration and agglomeration of HCV risk groups are expected to be present, such as large cities.[15,32]

Considering the Wilson & Jungner criteria and the new insights regarding these criteria posed by the WHO in 2008, targeted hepatitis C screening campaigns meet all the required conditions for implementation of a screening programme.[33,34] This underlines

the importance of the implementation of hepatitis C campaigns and should stimulate implementation in all countries were these required conditions can be met.

When implementing a HCV campaign, it is worthwhile considering integrating screening for related diseases. Hepatitis B virus (HBV) and HIV are infectious diseases which have similar high-risk populations as HCV. Recent studies regarding HBV and HIV screening in high-risk populations indicate that screening programmes for HBV and HIV are likely to be cost-effective.[35–37] Considering the overlapping target populations, combining these diseases in one screening campaign could reduce total campaign costs and increase the effectiveness compared to the implementation of individual strategies.

Developments in treatment for HCV infection are rapidly evolving. Treatment will become more effective after shorter treatment duration and improvements in the use of short-term indications of non-response will lead to shorter treatment of those who do not reach sustained viral response.[4] In addition new medical treatments such as polymerase inhibitors and protease inhibitors are expected to dramatically improve cure rates.[38,39] Even though these medications will initially come at a high cost, the shorter duration of treatment, higher success rates and increased quality of life during treatment, are expected to improve cost-effectiveness for HCV case finding in the near future.

The constantly changing composition of the Dutch population might also influence the cost-effectiveness of future hepatitis C campaigns. Assuming that the largest increase in unidentified HCV carriers is due to the increasing immigrant population, the prevalence of HCV in The Netherlands is expected to increase.[8,40] This will result in a lower ICER of case finding strategies, assuming that the campaign in its current form will be as successful in reaching immigrants as it is in reaching other inhabitants.

Conclusion

The incremental cost-effectiveness ratio (ICER) of implementing a nationwide HCV campaign with complementary support for primary care is estimated at €11,297 per QALY. The ICER of implementing a national campaign aimed at the identification of HCV carriers among HDU is estimated at €7,321 per QALY. Considering a Dutch cut-off point of €20,000 as a favourable cost-effectiveness ratio, both campaigns can be considered as cost-effective strategies for improving case finding and preventing future complications of HCV.[28] Since the pilot HCV campaign without primary care practice support did not result in improved case finding of HCV carriers, a support programme for primary

care practices is vital for achieving cost-effectiveness in a HCV campaign aimed at the general public.

Acknowledgements
The cost-effectiveness evaluation of the HCV campaigns was funded by The Netherlands Organization for Health Research and Development (ZonMw).
No conflict of interest is to be reported.

Supplementary Information

Cost-effectiveness of targeted screening for hepatitis C in the Netherlands

Webtable 1. Costs of diagnostic and therapeutic process and range / distribution used for the uncertainty analysis

Diagnostic tests and consultation before treatment	Distribution function	Costs in €
First consultation GP to determine need for anti-HCV testing *	PERT (mean ± 10%)	9.00
First counselling hard drug user to determine need for anti-HCV testing[21]	PERT (mean ± 10%)	21.17
Immunoassay (EIA) screening tests + fee †	PERT (mean ± 10%)	25.30
Polymerase Chain Reaction (PCR) + fee †	PERT (mean ± 10%)	120.10
Second consultation GP in case of positive test *	PERT (mean ± 10%)	9.00
Immunoassay (EIA) screening tests + fee † + costs nurse	PERT (27; 30; 33)	30.00
Second counselling hard drug user positive test[21]	PERT (mean ± 10%)	28.23
Second counselling hard drug user negative test[21]	PERT (mean ± 10%)	7.06
Total cost of medication and diagnostic procedures during treatment per patient after correcting for early discontinuation of treatment[22,26] ‡	**Distribution function**	**Costs in €**
Genotype 1 and 4 (48 weeks)	PERT (mean ± 10%)	15,772
Genotype 2 and 3 (24 weeks)	PERT (mean ± 10%)	9,582

** Julius Center for Health Sciences and Primary Care, † Laboratory MMC Amersfoort, ‡ Costs are adjusted for the current standard treatment (peg-interferon alfa and ribavirin) and include diagnostic monitoring, occurrence of side effects and early discontinuation of treatment*

Webtable 2. Clinical characteristics and range / distribution used in uncertainty analysis

Parameter	Distribution function	Value
General population		
Number of anti-HCV positive tests[14]	BETA (3; 112) * 115	3
Natural course - probability of chronic HCV infection[3]	UNIFORM (74%; 86%)	80%
Percentage infections of genotype 2 or 3[11]	BETA (45; 73)	38.1%
Referral rate[25]	PERT (50%; 70%; 90%)	70%
Percentage eligible and accepting treatment, genotype 1 or 4[5]	PERT (mean ± 10%)	55%
Percentage eligible and accepting treatment, genotype 2 or 3[5]	PERT (mean ± 10%)	60.5%
Percentage of eligible patients starting treatment in second year *	PERT (10%; 20%; 30%)	20%
Hard drug users		
Number of anti-HCV positive tests[16]	BETA (57; 129) * 186	57
Probability of spontaneous clearance of virus[16]	1-BETA (49; 8)	14%
Percentage infections of genotype 2 or 3[11]	BETA (22; 33)	40.0%
Referral rate[16]	BETA (35; 14)	71.43%
Percentage eligible and accepting treatment[16]	BETA (13;22)	37.14%
Equal for general population and hard drug users		
Annual probability of identification in case of no campaign †	PERT (1.1%; 1.2%; 1.3%)	1.2%
Average age at testing, for drug users and the general population[11]	PERT (37; 44.3; 51.6)	44.3
Probability of successful treatment, genotype 1 or 4, mild or moderate hepatitis[5]	PERT (mean ± 5%)	54%
Probability of successful treatment, genotype 1 or 4, cirrhosis[5]	PERT (mean ± 5%)	24%
Probability of successful treatment, genotype 2 or 3, mild or moderate hepatitis[5]	PERT (mean ± 5%)	94%
Probability of successful treatment, genotype 2 or 3, cirrhosis[5]	PERT (mean ± 5%)	48%
Fraction of HCV carriers with mild hepatitis at time of testing[6]	Dirichlet	46% (21/46)
Fraction of HCV carriers with moderate hepatitis at time of testing[6]	Dirichlet	43% (20/46)
Fraction of HCV carriers with cirrhosis at time of testing[6]	Dirichlet	11% (5/46)

** Database infectious diseases UMC Utrecht, † Based on Dutch prevalence and monitoring data.[7,8,24]*

Webtable 3. Costs of countrywide campaign and range/distribution used for uncertainty analysis

Campaign		Costs in €
General campaign *		
Total costs of a 4 month national campaign		610,373
Support campaign * † ‡ ¶	PERT (mean ± 10%)	1,261,470
Drug users campaign Ω	PERT (mean ± 10%)	156,443

** the Netherlands Institute for Health Promotion and Disease Prevention (NIGZ), † Julius Center for Health Sciences and Primary Care, ‡ Dutch College of General Practitioners (NHG), ¶ Raedelijn, Ω the National Institute of Mental Health and Addiction in the Netherlands (Trimbos institute) and the Mainline foundation*

Model parameters with lower and upper limits regarding transition probabilities, treatment efficacy, quality of life data and costs are taken from Siebert U, et al. ´Cost effectiveness of peginterferon alpha-2b plus ribavirin versus interferon alpha-2b plus ribavirin for initial treatment of chronic hepatitis C.´ Gut 2003 March; 52:425-32.`

Webtable 4. Sensitivity ranking – most influential parameters

Sensitivity ranking (rank regression) - support campaign	SRC
10 most influential parameters	
Number of cases found	- 0.64
Referral rate	- 0.15
Percentage genotype 2 or 3	- 0.09
State of hepatitis at identification - moderate hepatitis	- 0.09
Transition probability; moderate hepatitis -> compensated cirrhosis	0.08
State of hepatitis at identification - mild hepatitis	0.08
Disease costs - cirrhosis	- 0.08
Transition probability; mild hepatitis -> moderate hepatitis	- 0.07
Chance of positive PCR in case of positive anti-HCV	- 0.06
Average age at testing	0.05

Sensitivity ranking – drug users campaign	SRC
10 most influential parameters	
Average age at testing	0.64
Percentage treated	- 0.30
Disease costs - cirrhosis	0.28
State of hepatitis at identification - mild hepatitis	0.24
Percentage genotype 2 or 3	- 0.21
Transition probability; moderate -> compensated cirrhosis	- 0.21
State of hepatitis at identification - moderate hepatitis	- 0.19
Incidence of HCC in cirrhotic patients	- 0.15
Transition probability; compensated cirrhosis -> diuretic sensitive ascites	- 0.14
State of hepatitis at identification - cirrhosis	- 0.12

References

1. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infectious Diseases 2005; 5: 558–567.
2. World Health Organisation. Hepatitis C: global prevalence. Weekly Epidemiological Record 1997; 72: 341–344.
3. Lauer GM, Walker BD. Hepatitis C virus infection. New England Journal of Medicine 2001; 345:41–52.
4. Manns MP, et al. The way forward in HCV treatment finding the right path. Nature Reviews Drug Discovery 2007; 6: 991–1000.
5. Thompson-Coon J, et al. Case finding for hepatitis C in primary care : a cost utility analysis. Family Practice 2006; 23: 393–406.
6. Foster GR, et al. Management of chronic hepatitis C: clinical audit of biopsy based management algorithm. British Medical Journal 1997; 315: 453–458.
7. Slavenburg S, et al. Prevalence of hepatitis C in the general population in the Netherlands. Netherlands Journal of Medicine 2008; 66: 13–17.
8. Kretzschmar MEE. The prevalence of hepatitis C in the Netherlands [in Dutch]. Bilthoven, the Netherlands, National Institute of Public Health and the Environment, 2004; publication number VWS-IGZ 2004/ 02 – Project V/210041.
9. Kok A, et al. Hepatitis C in the Netherlands: sparse data on the current prevalence and the necessity for epidemiological studies and innovative methods for detecting infected individuals [in Dutch]. Nederlands Tijdschrift voor Geneeskunde 2007; 151:2367–2371.
10. Health Council of the Netherlands. Committee on hepatitis C. Detection and treatment of people with hepatitis C. Rijswijk : Health Council of the Netherlands, 1997; publication no. 1997/19.
11. de Vries MJ, te Rijdt B, van Nieuwkerk CM. Transmission of hepatitis C genotypes in the Netherlands amongst recently genotyped patients. Netherlands Journal of Medicine 2008; 66: 40–41.
12. Frank C, et al. The role of parenteral antischistosomal therapy in the spread of hepatitis C virus in Egypt. Lancet 2000; 355: 887–891.
13. Meltzer MI. Introduction to health economics for physicians. Lancet 2001; 358: 993–998.
14. Helsper CW, et al. A support programme for primary care leads to substantial improvements in the effectiveness of a public hepatitis C campaign. Family Practice 2010; 27: 328–332.
15. Laar van MW, et al. National drug monitor 2007. Utrecht, The Netherlands, Trimbos Institute. WODC research and documentation centre, 2008, publication no. AF0809.
16. Veen van der C, Hoogenboezem G, Breemer J. Education campaign aimed at hard drug users. Results of a pilot study [in Dutch]. Verslaving : Tijdschrift over Verslavingsproblematiek 2009; 5: 61–71.
17. Siebert U, et al. Cost effectiveness of peginterferon alpha-2b plus ribavirin versus interferon alpha-2b plus ribavirin for initial treatment of chronic hepatitis C. Gut 2003; 52: 425–432.
18. StatLine – Statistics Netherlands. (http://statline.cbs.nl/StatWeb/publication/?VW=T&DM=SLNL&PA=60020&LA=NL) [in Dutch]. Accessed 6 October 2006.
19. Smyth B, Fan J, Hser YI. Life expectancy and productivity loss among narcotics addicts thirty-three years after index treatment. Journal of Addictive Diseases 2006; 25: 37–47.
20. Organisation for Economic Cooperation and Development (OECD). Health Data 2007 (CD-ROM), 2007.
21. Breemer J, et al. Pre- and post-test counselling of hepatitis C, HIV and hepatitis B. Test protocol. Project active testing in addiction care and social shelter [in Dutch]. Rotterdam, The Netherlands: GGD Rotterdam-Rijnmond 2007.
22. Veldt B. Long-term clinical outcome of treatment for chronic hepatitis C [dissertation]. Rotterdam, the Netherlands: Rotterdam University, 2008, 52 pp.

23. Rodenburg-van Dieten H. Guidelines for farmacoeconomic research [in Dutch]. Diemen, the Netherlands: College voor Zorgverzekeringen, 2006, publication number FARM 24088606.
24. Op de Coul E, Bosman A, van de Laar M. Surveillance of hepatitis C in the Netherlands, 1992–2002 [in Dutch]. Infectieziekten Bulletin 2003; 9: 323–328.
25. de Jong DJ, et al. Referral of hepatitis C virus seropositive patients in primary care in the Netherlands. Netherlands Journal of Medicine 2008; 66: 42–43.
26. The Health Care Insurance Board (CVZ). Farmacotherapeutic Compass database (http://www.fk.cvz.nl/). Accessed 8 July 2008.
27. Statistics Netherlands (CBS). CBS table : Population per region subdivided to country and gender Database (http://statline.cbs.nl/StatWeb/). Accessed 1 January 2006.
28. Berg van den M, et al. Cost-effectiveness of prevention: opportunities for public health policy in the Netherlands [in Dutch]. Nederlands Tijdschrift voor Geneeskunde 2008; 152: 1329–1334.
29. Castelnuovo E, et al. The cost-effectiveness of testing for hepatitis C in former injecting drug users. Health Technology Assessment 2006; 10: xiii–iv, ix–xii, 1–93.
30. Stein K, et al. Screening for hepatitis C in injecting drug users : a cost utility analysis. Journal of Public Health (Oxford) 2004; 26: 61–71.
31. Sroczynski G, et al. Long-term effectiveness and cost-effectiveness of screening for hepatitis C virus infection. European Journal of Public Health 2009; 19: 245–253.
32. Statistics Netherlands (CBS). CBS table : Population of the Netherlands on first of January; age, country of birth and region (http://statline.cbs.nl/StatWeb/). Accessed 16 September 2009.
33. Wilson JMG, Jungner G. Principles and practice of mass screening for disease. Boletı´n de la Oficina Sanitaria Panamericana 1968; 65: 281–393.
34. Andermann A, et al. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. Bulletin of the World Health Organization 2008; 86: 317–319.
35. Veldhuijzen IK, et al. Screening and early treatment of migrants for chronic hepatitis B virus infection is cost-effective. Gastroenterology 2010; 138: 522–530.
36. Paltiel AD, et al. Expanded screening for HIV in the United States – an analysis of cost-effectiveness. New England Journal of Medicine 2005; 352: 586–595.
37. Bozzette SA. Routine screening for HIV infection timely and cost-effective. New England Journal of Medicine 2005; 352: 620–621.
38. Soriano V, Peters MG, Zeuzem S. New therapies for hepatitis C virus infection. Clinical Infectious Diseases 2009; 48: 313–320.
39. Zeuzem S. Interferon-based therapy for chronic hepatitis C: current and future perspectives. Nature Clinical Practice Gastroenterology & Hepatology 2008; 5: 610–622.
40. Statistics Netherlands (CBS). CBS table : immigration and emigration (http://statline.cbs.nl/StatWeb/). accessed 16 September 2009.

Chapter 3.2

´Real-life´ costs of successful treatment, relapse and non-response in patients treated for HCV infection in the Netherlands

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Abstract

Introduction: Hepatitis C virus infection is a serious health threat in today's society. Improved identification strategies have increased the number of patients undergoing the expensive treatment with ribavirin and peg-interferon, inducing a substantial economic burden.

Methods: In a retrospective cohort study in three treatment centres in the Netherlands, files of patients treated between 2001 and 2010 were systematically searched for all cost-inducing treatment details. Costs of treatment resulting in sustained viral response (SVR), relapse, non-response and the costs per cured patient were specified for genotype (GT) and treatment setting. Determinants of costs were determined by multivariate linear regression.

Results: The mean 'real-life' treatment costs excluding side-effects for GT1/4 and GT2/3 were approximately €12,900 and €9,900 for all patients, €15,500 and €10,100 for treatment resulting in SVR and €16,800 and €12,100 for relapse respectively. Costs per cured patient were €28,500 and €15,400 respectively. The costs of non-response were approximately €8,000 for all GTs. Costs of side-effects can be high and are mainly caused by incidental treatment for neutropenia. Medication is the main component of treatment costs. Treatment costs were higher in the academic setting due to longer duration and higher costs of side-effects. Regression analysis confirms duration as the main determinant of treatment costs excluding side-effects.

Conclusion: The ´real-life´ costs of treatment are mainly determined by treatment duration, medication costs and costs of side-effects. The costs of unsuccessful treatment are considerable as are the costs of side-effects. Therefore, future research should aim at increasing SVR-rates, reducing treatment duration and preventing side-effects.

Introduction

Due to its serious long term complications, hepatitis C virus (HCV) infection is increasingly recognized as a serious health threat in today's society. An estimated 123 to 170 million people have been infected globally.[1,2] In the Netherlands, this number is estimated to be between 15,000 and 60,000.[3,4] An infection with HCV leads to chronic hepatitis in 80% of cases, of which 20% develop liver cirrhosis after 20 to 30 years. Of those with cirrhosis, approximately 5% develop hepatocellular cancer.[5] As a consequence of these severe long term complications, HCV is considered responsible for 50%–76% of all patients with liver cancer and two-thirds of all liver transplants in the Western world.[6]
The lack of clinical signs and low awareness among the general public and medical professionals have held back detection rates considerably, but in the past decade several successful identification strategies have been developed.[7,8] This has led to an increased number of patients eligible for- and undergoing treatment, causing a substantial economic burden on society. Current success rates for treatment are dependent on genotype. HCV infections have been found in 7 genotypes of which genotype 1 to 4 are responsible for over 98% of the infections in the Netherlands.[9,10] Of the patients infected with genotype 1 and 4, approximately 50% can attain sustained viral response (SVR), which means the disease has been cured. The majority of patients infected with these genotypes require 48 weeks of treatment. For genotype 2 and 3 the treatment success rate is more favourable at approximately 80% after 24 weeks of treatment.[11]
Costs for HCV treatment result from several components. Direct medical costs result from professional workload, hospital costs, diagnostic testing, medication use and costs of side-effects. Indirect costs result from societal burden, such as productivity losses associated with absence from work.

A national guideline for the treatment of chronic hepatitis C was developed in 2008, initiated by the Netherlands Association of Gastroenterologists and Hepatologists (Nederlandse Vereniging van Maag Darm Lever artsen).[12] This guideline provides recommendations for the initial evaluation, the choice of the therapy and the required follow-up during and after therapy. This guideline aims to provide uniformity in treatment and a recent study has demonstrated that approximately 85% of treating medical specialists in gastroenterology, hepatology and internal medicine in the Netherlands adhere to the guidelines.[13]

The costs of treatment can diverge considerably as a result of varying treatment schedules and disease and patient characteristics. In this study we aim to assess the ´real-life´ costs of successful HCV treatment, relapse after treatment, non-response and

the costs per cured patient in the Netherlands. In addition, we aim to identify the most important determinants of these costs.

Methods

A retrospective cohort study was performed in three main HCV treatment centres in the Netherlands (two academic, one non-academic). The files of all patients treated for HCV between 2001 and 2010 were systematically searched for details of treatment. Exclusion criteria were: treatment other than ribavirin and peg-interferon, previous HCV treatment, HIV co-infection, unclosed files, excessive missing data (e.g. due to change of treatment institution) and no information available on treatment outcome. In close collaboration with the treating physicians, the data were extracted anonymously from the electronic and paper patient files. In these files all cost inducing elements were systematically extracted. These include the number of consultations, admissions to the hospital and length of stay, medication use, number and type of diagnostic tests performed, use of specialized homecare (e.g. 'Pegassist' or 'HepaZorg') and other registered use of hospital facilities. Side-effects were recorded based on the available reporting in patient files and additional diagnostic testing or treatment outside of the protocol related to side-effects known for HCV treatment. All data from one month before the beginning of drug treatment until the evaluation of treatment success at 24 weeks after drug treatment had ended were included in the analyses. Diagnostic testing as recommended in the national protocol and performed less than one year previous to the beginning of drug treatment was also taken into account. The costs resulting from the aforementioned treatment aspects were retrieved from the financial departments of the treating centres and the Dutch Health Care Insurance Board.[14] The latter costs are standardized cost prices that are recommended for use in health economic evaluations. Indirect costs, such as absence at work due to sickness, were not included in the calculations. Hence, the current study takes a healthcare perspective and estimates costs for 2010.

Mean treatment costs were determined for the different treatment outcomes and linked to the available patient and treatment characteristics. In addition, the 'costs per cure' were calculated by dividing the sum of treatment costs of all patients by the number of patients attaining SVR. The latter provides an indication of the average investment required for curing disease in one patient. Patient and treatment characteristics include age, gender, relevant life style such as known hard drug use, presence of co-infections such as HBV, genotype, liver damage based on the Metavir classification (determined by biopsy or fibroscan), treatment duration and treatment setting.[15] In addition, the theoretical costs resulting from a full term and strictly followed treatment schedule according

to the national treatment protocol were calculated as background information.
To detect the most important patient and treatment characteristics determining treatment costs, we performed multivariate linear regression. This analysis was performed in two steps, the first excluding and the second including 'severity of liver damage' as a parameter in the model. The first analysis was performed for all 85 treated patients and repeated for both groups of genotypes. Since information on severity of liver damage could only be found in the files of 59 patients (40 with GT1/4 and 19 with GT2/3), the impact of this parameter on treatment costs was determined in a separate analysis.

Results

From the study period, 104 patient files were available for assessment in the three treatment centres. The files of 85 patients (81.7%) were suitable for analyses. The main reasons for exclusion were a positive HIV-status, unclosed files or change of treating institution. Baseline characteristics are demonstrated in table 1. The mean costs and duration of HCV treatment and the corresponding standard deviations (SD), specified for patients with GT1/4 and GT2/3 and for treatment result, are shown in table 2. This table also includes costs per cure. Figure 1 demonstrates the different treatment costs for different outcomes, specified for costs of diagnostic testing, medication, hospital costs and side-effects.
We found a substantial variability in costs of side-effects, which was caused by only a few patients with very high costs and therefore largely determined by chance. Therefore, the primary presentation of costs is done excluding side-effects with the costs of side-effects presented separately.

Costs of treatment for all patients
The mean costs of treatment for all treated patients with genotype 1/4, excluding costs of side-effects, were approximately 12,900 euro after a mean treatment duration of 223 days (31.8 weeks). Mean costs of side-effects were approximately 2,200 euro. The nature of the side-effects responsible for these costs is provided in the paragraphs below.
The mean treatment costs for all patients with genotype 2/3, excluding costs of side-effects, were approximately 9,900 euro after a mean treatment duration of 174 days (24.8 weeks). Mean costs of side-effects were approximately 2,400 euro.
The theoretical costs of a full term treatment based on the national protocol were 19,189 for GT1/4 and 11,204 for GT2/3.

Table 1. Patient characteristics in different settings

	All settings	Academic Infectious diseases dept.	Academic Gastro-enterology dept.	Non-academic Infectious diseases dept.
Genotype 1 & 4				
Number of patients	51	15	14	22
Gender – male	40 (78%)	12 (80%)	10 (71%)	18 (82%)
Mean age	46.4	46.1	44.1	48.0
Liver damage known †	40 (78%)	14 (93%)	13 (93%)	13 (59%)
– no scarring	12 (30%)	4 (29%)	4 (31%)	4 (31%)
– minimal scarring	7 (18%)	2 (14%)	2 (15%)	3 (23%)
– moderate scarring	9 (23%)	3 (21%)	3 (23%)	3 (23%)
– bridging fibrosis	6 (15%)	5 (36%)	1 (8%)	0 (0%)
– cirrhosis or advanced scarring	6 (15%)	0 (0%)	3 (23%)	3 (23%)
Sustained viral response	27 (53%)	9 (60%)	7 (50%)	11 (50%)
Mean treatment duration in days (SD)	223 (120)	260 (144)	225 (103)	196 (110)
Genotype 2 & 3				
Number of patients	34	13	7	14
Gender – male	26 (76%)	9 (69%)	6 (86%)	11 (79%)
Mean age	42.5	39.8	48.4	42.1
Liver damage known †	19 (56%)	9 (69%)	7 (100%)	3 (21%)
– no scarring	5 (26%)	5 (56%)	0 (0%)	0 (0%)
– minimal scarring	5 (26%)	3 (33%)	2 (29%)	0 (0%)
– moderate scarring	4 (21%)	1 (11%)	2 (29%)	1 (33%)
– bridging fibrosis	1 (5%)	0 (0%)	1 (14%)	0 (0%)
– cirrhosis or advanced scarring	4 (21%)	0 (0%)	2 (29%)	2 (67%)
Sustained viral response	25 (73%)	11 (85%)	3 (43%)*	11 (79%)
Mean treatment duration in days (SD)	174 (70)	190 (69)	156 (99) *	167 (56)

** Low number due to two dropouts with early side-effects.*
† Based on Metavir classification for liver damage; 1. no scarring, 2. minimal scarring, 3. scarring has occurred and extends outside the areas in the liver that contains blood vessels, 4. bridging fibrosis is spreading and connecting to other areas that contain fibrosis, 5. cirrhosis or advanced scarring of the liver.[15]

Costs of successful treatment

SVR was attained in 53% of patients with GT1/4 and 74% of patients with GT2/3. The mean costs of treatment resulting in SVR for patients with genotype 1/4, excluding costs of side-effects, were approximately 15,500 euro after a mean treatment duration of 285 days (40.7 weeks). Mean costs of side-effects were approximately 3,500 euro. The considerable costs of side-effects were generated by six patients in the academic setting for whom 5,818 to 41,543 euro was spent on the treatment of side-effects. These

Table 2. Costs (€) and duration (days) of treatment - specified for treatment result

	All patients †	SVR †	Relapse †	Non-response †	Costs ‡ per cure
	Mean *SD*	Mean *SD*	Mean *SD*	Mean *SD*	
Genotype 1 & 4	N = 51 *	N = 27	N = 7	N = 15	
Costs excluding side-effects	12,856 *6,060*	15,483 *4,980*	16,800 *5,466*	7,566 *2,840*	24,283
Costs including side-effects	15,104 *9,010*	19,032 *9,293*	18,464 *5,502*	8,014 *2,833*	28,529
Mean treatment duration in days	223 *120*	285 *90*	287 *94*	108 *53*	
Costs if national protocol completed		19,189			
Genotype 2 & 3	N = 34	N = 25	N = 5	N = 2	
Costs excluding side-effects	9,911 *3,051*	10,095 *2,574*	12,068 *3,490*	8,065 *184*	13,479
Costs including side-effects	11,324 *7,175*	10,757 *3,392*	18,340 *16,151*	8,078 *202*	15,400
Mean treatment duration in days	174 *70*	174 *55*	235 *92*	147 *30*	
Costs if national protocol completed		11,204			

** Four patients, two with GT1/4 and two with GT2/3, stopped treatment due to side-effects after a mean duration of 31.5 days and mean treatment costs of 3,796 euro. These patients are only included in the "All patients" group.*
† Mean treatment costs and mean treatment duration of patients with the indicated outcome.
‡ Costs per cure were calculated by dividing the sum of treatment costs of all patients by the number of patients attaining SVR. This provides an indication of the investment made for curing disease in one patient.

high costs result from treatment with pegfilgrastim for neutropenia and epoetin alfa for anaemia.

The mean costs of treatment resulting in SVR for those with genotype 2/3, excluding costs of side-effects, were approximately 10,100 euro after a mean treatment duration of 174 days (24.8 weeks). Mean costs of side-effects were lower at approximately 650 euro. Costs per cure for patients with GT1/4 were approximately 28,500 euro including side-effects and 24,300 euro excluding side-effects. Costs per cure for patient with GT2/3 were approximately 15,400 euro including side-effects and 13,500 euro excluding side-effects.

Costs of unsuccessful treatment

The mean costs of treatment of patients with GT1/4 resulting in relapse after initial success excluding side-effects, were 16,800 euro after a treatment duration of 287 days (41.0 weeks). Mean costs for side-effects were approximately 1,700 euro. The mean costs of treatment for patients with GT1/4 resulting in non-response excluding side-effects, were 7,600 euro after a treatment duration of 108 days (15.4 weeks). Mean costs for side-effects were approximately 450 euro.

The mean costs of treatment of patients with GT2/3 resulting in relapse after initial success excluding side-effects, were 12,100 euro after a treatment duration of 235 days (33.6 weeks). Mean costs of side-effects were approximately 6,300 euro. These costs of side-effects were high due to the treatment of one patient in the academic setting, who received filgrastim for neutropenia costing approximately 31,000 euro. The mean costs of treatment for patients with GT2/3 resulting in non-response excluding side-effects, were 8,100 euro after a treatment duration of 147 days (21.0 weeks). Mean registered costs for side-effects were only 13 euro in this group.

Determinants of treatment costs

As demonstrated by the aforementioned findings, costs of side-effects were substantial and consequently an important component of total treatment costs. As demonstrated in figure 1, the primary constituent of the treatment costs were costs of medication.

The multivariate linear regression analyses indicated that treatment duration was the sole statistically significant determinant of treatment costs in all separate analyses (p-value < 0.001). Genotype, gender, age, known injecting drug use, treatment setting, somatic comorbidity, psychiatric comorbidity and severity of liver damage were not independently associated with treatment costs (p-value >0.05). Tables 3 and 4 demonstrate the full results of the multivariate analyses.

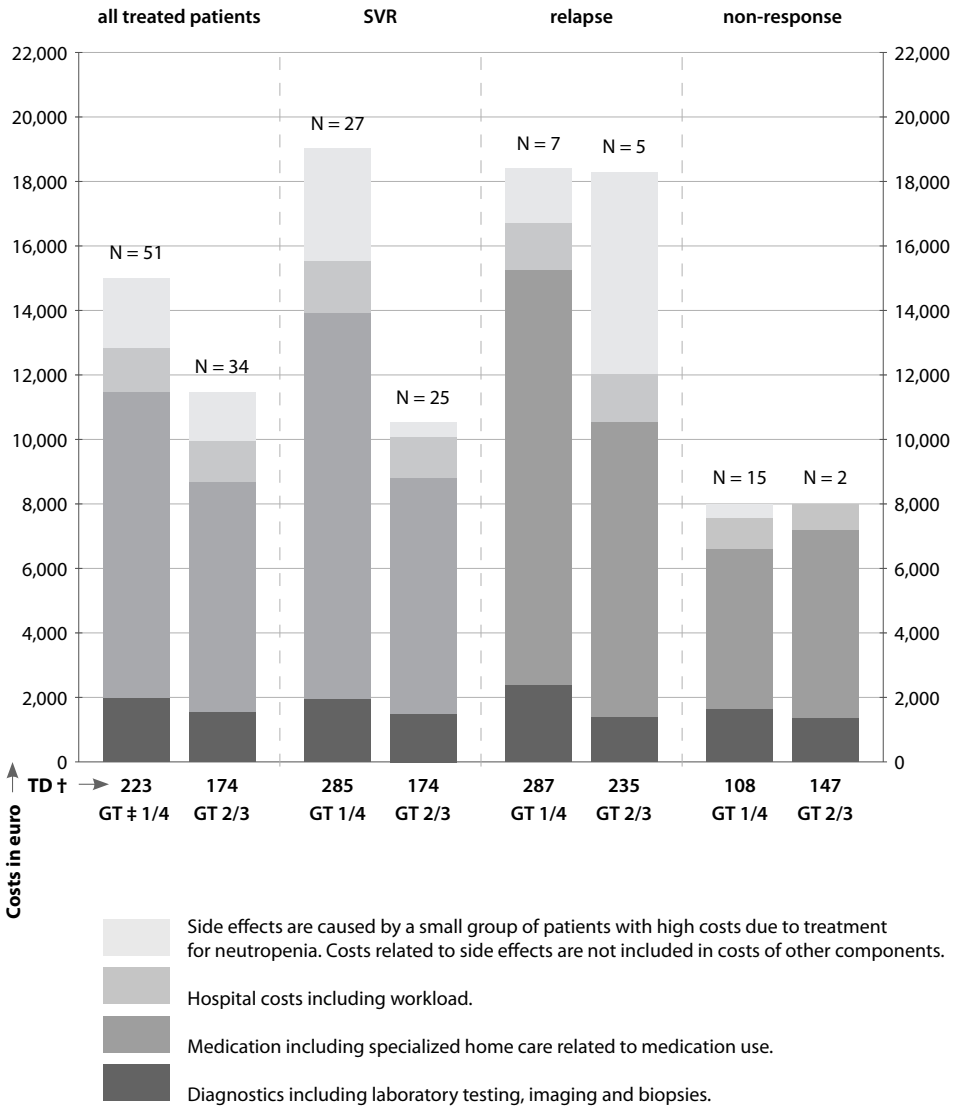
Treatment setting

Table 5 provides an overview of the mean treatment costs specified for treatment setting and outcome.

In the academic setting costs per cure were 33% higher for GT1/4 and 43% higher for GT2/3, than in the non-academic setting. After adjustment for costs of side-effects, this difference remained at 14 and 21%. For GT2/3, this is mainly the result of the low SVR rate in one of the academic centres in which only 43% (3 out of 7) patients reached SVR. This low SVR rate was caused by two early drop-outs due to side-effects and two patients who relapsed.

An additional explanation for the higher costs in the academic setting is the longer mean treatment duration. For GT1/4, the number of 'treatment days per cure' in the academic setting is 441 days versus 392 in the non-academic setting (difference 12%). For GT2/3

Figure 1. Components of costs of treatment, specified for treatment outcome*



**Four patients, two with GT1/4 and two with GT2/3, stopped treatment due to side-effects after a mean duration of 31.5 days and total treatment costs of €3,796. These patients are only included in the 'all patients' group. †TD: treatment duration in days. ‡GT: genotype.*

Table 3. Multivariate linear regression – determinants of treatment costs excluding side-effects in a model excluding liver damage

	Unstandardized Coefficients (B)	Standardized Coefficients (Beta)	P value
All patients - (N = 85)			
Genotype2	-809.6	-0.043	0.231
Genotype3	-442.0	-0.039	0.315
Genotype4	-11.1	-0.001	0.985
Treatment result	51.6	0.009	0.836
Gender (1=male)	289.6	0.023	0.519
Age	18.0	0.039	0.272
Treatment duration (days)	47.4	0.950	0.000
Known injecting drug use (1=yes)	-301.2	-0.029	0.436
Treatment setting (1=non-academic)	-494.3	-0.047	0.171
Comorbidity Somatic	-556.2	-0.037	0.295
Comorbiditeit psychiatric	-244.5	-0.022	0.524
(Constant)	*1660.8*		*0.149*
(Explained variance - R^2)	*0.927*		
Genotype 1 & 4 - (N = 51)			
Treatment result	662.7	0.108	0.082
Gender (1=male)	657.7	0.045	0.267
Age	10.7	0.022	0.596
Treatment duration (days)	53.0	1.048	0.000
Known injecting drug use (1=yes)	-291.5	-0.024	0.547
Treatment setting (1=non-academic)	-446.9	-0.037	0.345
Comorbidity Somatic	-794.9	-0.048	0.243
Comorbiditeit psychiatric	-213.4	-0.017	0.665
(Constant)	*-646.9*		*0.663*
(Explained variance - R^2)	*0.946*		
Genotype 2 & 3 - (N = 34)			
Treatment result	-603.3	-0.170	0.060
Gender (1=male)	504.4	0.071	0.407
Age	-2.1	-0.006	0.935
Treatment duration (days)	36.5	0.838	0.000
Known injecting drug use (1=yes)	68.2	0.011	0.902
Treatment setting (1=non-academic)	-419.6	-0.069	0.369
Comorbidity Somatic	829.2	0.089	0.291
Comorbiditeit psychiatric	-763.6	-0.112	0.151
(Constant)	*4389.1*		*0.005*
(Explained variance - R^2)	*0.870*		

Table 4. Multivariate linear regression – determinants of treatment costs excluding side-effects in a model including liver damage

	Unstandardized Coefficients (B)	Standardized Coefficients (Beta)	P value
All patients - (N = 59)			
Genotype2	-1319.7	-0.059	0.181
Genotype3	-206.6	-0.016	0.757
Genotype4	-77.3	-0.004	0.921
Treatment result	257.1	0.045	0.472
Gender (1=male)	416.5	0.033	0.483
Age	14.8	0.031	0.512
Treatment duration (days)	49.2	0.986	0.000
Known injecting drug use (1=yes)	-264.1	-0.023	0.602
Treatment setting (1=non-academic)	-856.3	-0.067	0.113
Comorbidity Somatic	-659.5	-0.042	0.379
Comorbiditeit psychiatric	-190.5	-0.016	0.729
Severity of liver damage	-107.2	-0.027	0.597
(Constant)	*1359.8*		*0.376*
(Explained variance - R^2)	*0.934*		
Genotype 1 & 4 - (N = 40)			
Treatment result	845.6	0.132	0.150
Gender (1=male)	845.6	0.058	0.305
Age	9.3	0.019	0.732
Treatment duration (days)	54.4	1.076	0.000
Known injecting drug use (1=yes)	-358.9	-0.028	0.577
Treatment setting (1=non-academic)	-574.8	-0.043	0.370
Comorbidity Somatic	-689.6	-0.039	0.524
Comorbiditeit psychiatric	-380.3	-0.029	0.593
Severity of liver damage	-114.9	-0.026	0.667
(Constant)	*-999.9*		*0.644*
(Explained variance - R^2)	*0.940*		
Genotype 2 & 3 - (N = 19)			
Treatment result	-565.1	-0.180	0.101
Gender (1=male)	-23.4	-0.004	0.976
Age	-36.6	-0.102	0.297
Treatment duration (days)	32.0	0.769	0.000
Known injecting drug use (1=yes)	387.9	0.065	0.614
Treatment setting (1=non-academic)	-1091.8	-0.135	0.207
Comorbidity Somatic	-291.1	-0.036	0.757
Comorbiditeit psychiatric	-1234.3	-0.171	0.156
Severity of liver damage	464.4	0.229	0.151
(Constant)	*5989.0*		*0.004*
(Explained variance - R^2)	*0.947*		

Table 5. Mean treatment costs (€) and duration specified for treatment setting and outcome

	All patients	SVR	Relapse	Non-response	Early stop	Costs per cure
Genotype 1 & 4	N = 51	N = 27	N = 7	N = 15	N = 2	
Costs excluding side-effects						
All patients	12,856	15,483	16,800	7,566	3,266	24,283
- non-academic	11,199	13,856	15,320	6,000	-	22,398
- academic	14,113	16,601	17,911	9,355	3,266	25,580
= gastroenterology	13,351	15,322	15,898	11,094	3,486	26,702
= infectious diseases	14,824	17,596	19,924	7,036	3,045	24,707
Costs including side-effects						
All patients	15,104	19,032	18,464	8,014	3,483	28,529
- non-academic	11,929	14,535	16,985	6,449	-	23,858
- academic	17,512	22,124	19,573	9,802	3,483	31,741
= gastroenterology	18,320	24,789	17,331	11,094	3,921	36,640 †
= infectious diseases	16,758	20,051	21,815	8,079	3,045	27,930
Mean treatment duration						
All patients	223	285	287	108	21	-
- non-academic	196	250	296	84	-	-
- academic	243	309	280	135	21	-
= gastroenterology	225	285	224	172	21	-
= infectious diseases	260	327	336	86	21	-
Genotype 2 & 3	N = 34	N = 25	N = 5	N = 2	N = 2	
Costs excluding side-effects						
All patients	9,911	10,095	12,068	8,065	4,061	13,479
- non-academic	9,480	9,154	12,045	7,935	-	12,066
- academic	10,212	10,834	12,083	8,195	4,061	14,589
= gastroenterology	9,701	11,125	13,203	-	4,061	22,635 *
= infectious diseases	10,488	10,754	9,843	8,195	-	12,394
Costs including side-effects						
All patients	11,324	10,757	18,340	8,078	4,110	15,400
- non-academic	9,755	9,503	12,050	7,935	-	12,415
- academic	12,422	11,742	22,534	8,221	4,110	17,745
= gastroenterology	15,109	13,261	28,879	-	4,110	35,253 *
= infectious diseases	10,975	11,328	9843	8,221		12,971
Mean treatment duration						
All patients	174	174	235	147	42	-
- non-academic	167	155	252	126	-	-
- academic	178	189	224	168	42	-
= gastroenterology	156	168	252	-	42	-
= infectious diseases	190	194	168	168	-	-

** High costs due to low SVR-rate (43% of total N=7, including 2 early drop-outs due to side-effects)*
† High costs due to large investment in treatment of a few patients for side-effects

this difference is 255 versus 213 days (difference 20%). The highest and lowest mean number of treatment days, correspond with the highest and lowest SVR rates.
The mean total costs of treatment for all patients were approximately 50% higher in the academic setting at 17,500 versus 12,000 euro in the non-academic setting. Adjustment for investments made for the treatment of side-effects reduces this difference to approximately 25% (14,100 vs 11,100 euro). This resembles the difference in treatment duration, which is also approximately 25% (243 vs 196). Consequently the treatment costs per day were similar at 58.1 euro in the academic setting, versus 57.2 euro in the non-academic setting. For treatment leading to SVR these costs were 54 euro (academic) and 55 euro (non-academic).

Discussion

Summary of findings
As expected, the mean 'real-life' costs for all patients treated for HCV excluding side-effects were higher for GT1/4 than for GT 2/3 (12,900 versus 9,900 euro). For treatment resulting in SVR these costs were slightly higher. Costs of treatment resulting in relapse were approximately 2,000 euro higher than those for a treatment resulting in SVR. Costs of non-response were approximately 8,000 euro for all genotypes. Costs per cured patient with GT1/4 and GT2/3 were approximately 28,500 euro and 15,400 euro (including side-effects). Costs of side-effects can be substantial due to treatment for neutropenia or anaemia, but differ considerably between patients. Treatment duration was the most important determinant of costs, of which the costs of medication were the primary constituent. Treatment costs were generally higher in the academic setting due to longer treatment duration and more money spent on the treatment of side-effects.

The finding that the higher costs in the academic setting result from longer duration is supported by the multivariate regression analyses which demonstrate that, when corrected for treatment duration, treatment setting is not associated with costs of treatment.
The higher costs of treatment for side-effects in the academic setting can in part be explained by the treatment used for anaemia. In the academic setting epoetin alfa was used in the treatment of anaemia, whereas in the non-academic setting the treatment was based on blood transfusions. The main difference in costs of side-effects however, results from the treatment of neutropenia with (peg)filgrastim. Since this treatment should only be initiated and supervised by physicians with relevant experience, availability of this specialized care in the different settings at the time of treatment could have been of influence. The readiness and possibilities to invest more in attaining SVR

could be another reason for the difference in costs of side-effects. However, the costs of side-effects and corresponding success rates of the different settings do not reflect this. Since the number of patients generating the costs of side-effects is low, the difference in costs of side-effects between settings could also be due to chance. The readiness and possibilities to invest more in realizing SVR also provides an explanation for the difference in treatment duration between the treatment settings. This is supported by the finding that longer treatment duration seemed to be related to increased success rate. Since our study was neither designed nor aimed to assess the determinants of treatment success, we did not test this relationship in detail.

A final explanation for the longer treatment duration and higher costs for side-effects in the academic setting are differences in baseline characteristics of the patient populations. In general, primary care physicians choose to send patients in whom a more complicated treatment is expected to more specialized settings such as the academic centres. In addition, less specialized medical specialists sometimes refer HCV patients who are difficult to treat to more specialized treatment centres. Due to the limited number of patients for whom liver damage could be determined and the lack of information on patient characteristics which could influence treatment success (such as BMI or ethnicity), we could not test this hypothesis.

Strengths and limitations

The main strength of our study is that it provides a 'real-life' overview of the costs of treatment as performed in daily practice instead of a theoretical profile prescribed by the protocol. This leads to a daily practice based estimation of treatment costs assessed in a 'real-life' population. Given the highly variable population treated for HCV and the various factors which could lead to treatment adjustment, we expect that our 'real-life' study provides a more reliable estimation of treatment costs than theory based estimations.

The main limitation is that the input for our calculations is restricted to the data that is registered in the patient files. This might have led to an underestimation of true costs, due to omissions. This underestimation is likely to be most relevant for side-effects, because files will only state what is substantial or complained about. Registrations of side-effects based on diagnostic testing outside the protocol will only detect side-effects for which additional diagnostic testing is needed. In addition, only side-effects for which it was certain that they were caused by the HCV treatment were registered as being a side-effect. Comorbidities existing previous to treatment and flaring up during treatment were not included because treatment could not be confirmed as the causal factor. This might lead to an underestimation of side-effects and its costs. Diagnostic testing is automatically reported by the hospital systems and costs of medication were calculated based on the initiated treatment and reported changes in medication dosage.

Therefore underestimation of costs for these determinants is expected to be minor.
Given the retrospective and therefore observational data collection, we had limited influence on registration of patient characteristics which are related to treatment outcome. Consequently we had incomplete knowledge of characteristics which could have provided more background on the reasons for longer treatment duration and higher costs of treatment, such as liver damage, specified psychiatric problems, BMI, race and alcohol dependency.

The fact that our data came from three treatment centres may limit the generalizability of the conclusions. However, HCV treatment is concentrated in a limited number of expertise centres and the three centres in our study cover most of the HCV treatment in the central and eastern region of the Netherlands.

Co-infection with HIV is a frequent problem in HCV patients, which could lead to different treatment costs. Because we did not have access to sufficient information in the files of patients with HIV co-infection, we had to restrict our study to the costs of treatment for HIV negative patients.

Conclusion

The "real-life" costs of HCV treatment are mainly determined by the costs of medication and side-effects and the duration of treatment. At present, these determinants and the costs of treatment for patients who are not treated successfully lead to a substantial financial investment needed to cure one patient. To reduce costs and improve cost-effectiveness of treatment, future research should be aimed at increasing SVR rates, reducing treatment duration and preventing side-effects.

Acknowledgements
We want to thank all staff of the involved treatment centres for their support in data-collection. This study was funded by the Netherlands Organisation for Health Research and Development (ZonMw).

Reference List

1. Hepatitis C: global prevalence. Wkly Epidemiol Rec 1997; 72(46):341-344.
2. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis 2005; 5(9):558-567.
3. Health Council of the Netherlands: Committee on hepatitis C. Detection and treatment of people with hepatitis C. 1997/19. 1997. Rijswijk.
4. Slavenburg S, Verduyn-Lunel FM, Hermsen JT, Melchers WJ, te Morsche RH, Drenth JP. Prevalence of hepatitis C in the general population in the Netherlands. Neth J Med 2008; 66(1):13-17.
5. Lauer GM, Walker BD. Hepatitis C virus infection. N Engl J Med 2001; 345(1):41-52.
6. World Health Organization (WHO). State of the art of vaccine research and development. Report number WHO/IVB/05.XX. 2011. Available from http://www.who.int/vaccine_research/documents/Viral_Cancers.pdf. 22-6-2011.
7. Helsper C.W., Borkent-Raven B.A., de Wit N.J., van Essen G.A., Bonten M.J.M., Janssen M.P. et al. Cost-effectiveness of targeted screening for hepatitis C in the Netherlands. Infection and Epidemiology 2010.
8. Zuure FR, Davidovich U, Coutinho RA, Kok G, Hoebe CJ, van den HA et al. Using mass media and the Internet as tools to diagnose hepatitis C infections in the general population. Am J Prev Med 2011; 40(3):345-352.
9. de Vries MJ, te Rijdt B., van Nieuwkerk CM. Transmission of hepatitis C genotypes in the Netherlands amongst recently genotyped patients. Neth J Med 2008; 66(1):40-41.
10. de Vries MJ, te RB, van Nieuwkerk CM. Genotype distribution amongst hepatitis C patients in The Netherlands. Neth J Med 2006; 64(4):109-113.
11. Manns MP, Foster GR, Rockstroh JK, Zeuzem S, Zoulim F, Houghton M. The way forward in HCV treatment--finding the right path. Nat Rev Drug Discov 2007; 6(12):991-1000.
12. de BJ, Buster EH, Gelderblom HC, Brouwer JT, de Knegt RJ, van Erpecum KJ et al. Treatment of chronic hepatitis C virus infection - Dutch national guidelines. Neth J Med 2008; 66(7):311-322.
13. Slavenburg S, Lamers MH, Roomer R, de Knegt RJ, van Oijen MG, Drenth JP. Current clinical care compared with new Dutch guidelines for hepatitis C treatment. Neth J Med 2009; 67(5):177-181.
14. Oostenbrink JB, Bouwmans C.A.M., Koopmanschap MA, Rutten FF, Jager J, institute for medical technology assessment EM. Standardisation of costs: the Dutch Manual for Costing in economic evaluations. [in Dutch; Handleiding voor kostenonderzoek: methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg] - Update 2004. 2004.
15. Theise ND. Liver biopsy assessment in chronic viral hepatitis: a personal, practical approach. Mod Pathol 2007; 20 Suppl 1:S3-14.

Chapter 3.3

Effectiveness and cost-effectiveness of a nation-wide campaign for awareness and case finding of hepatitis C in the Netherlands

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Abstract

Introduction: Hepatitis C virus infection (HCV) is a serious disease that at present can be treated successfully in the majority of patients. Because HCV is severely underdiagnosed, the need for increased awareness and improved case finding is pressing. With this purpose a nationwide HCV campaign was implemented in the Netherlands targeting risk groups in the general public ('public intervention') and hard drug users (HDU) in addiction care ('HDU intervention').

Methods: The 'public intervention' consisted of health education though mass media and instruction of health care professionals. It was implemented in 6 large cities in the Netherlands and lasted for 6 months. All addiction care centres in the Netherlands participated in the 'HDU intervention', which consisted of individual HCV consultation and testing of HDU and lasted for 18 months. The change in the number of anti-HCV tests performed in the intervention period as compared to control regions or previous years was the primary endpoint. Cost-data were registered in close cooperation with the involved organizations. A Markov-chain model was used to estimate the incremental cost-effectiveness ratio (ICER) for both interventions.

Results: The 'public intervention' resulted in the identification of 38 HCV carriers. The resulting ICER was €16,673 (95%CI: €6,774-€21,907,423) per quality adjusted life year (QALY) gained. The 'HDU intervention' identified 257 HCV carriers, resulting in an ICER of €8,245 (95%CI: €6,109-€11,349) per QALY gained. Probabilistic sensitivity analysis showed a probability of 63% that the public campaign exceeds the Dutch threshold for cost-effectiveness of €20,000. The maximum estimated ICER for the 'HDU intervention' was €15,008 and was therefore certainly cost-effective.

Conclusion: In a nationwide campaign aimed at improving HCV awareness and case finding, an intervention aimed at hard drug users was clearly cost-effective. An intervention targeting the general population showed only a modest effect. Because the combined results from this nationwide campaign do not sufficiently counter the problem of underdiagnosis of HCV, new case finding strategies for HCV need to be developed.

Introduction

Hepatitis C virus infection (HCV) is an infectious liver disease that can lead to serious long-term complications. Even though approximately 170 million people are infected worldwide, the disease remains relatively unknown among the general public and medical professionals.[1,2] HCV infection generally does not cause clinical symptoms before its complications occur. Therefore identification of those infected is often delayed or neglected. After 20 to 30 years, approximately 25% of those chronically infected will develop liver cirrhosis, resulting in hepatocellular carcinoma in 5% of these cases.[3] As a consequence, HCV is held responsible for 50% to 76% of all liver cancer cases and two-thirds of all liver transplants in the Western world.[4]
In Europe (including Russia) 11.3 to 14.7 million people are infected with HCV. Prevalence rates in the population vary from approximately 0.5% in North-West Europe to over 7% in parts of South-East Europe.[5] In the Netherlands the prevalence is estimated at 0.1 to 0.4% (16,000-64,000 persons) and up to 0.6% in highly urbanized areas.[6,7] So far only a minority of those infected has been diagnosed.[5,8-10] The diagnosis rate of HCV varies across Europe from 2.7% in Poland to 80% in Sweden.[5] The blood-bound pathway of HCV infection, has led to the identification of several risk groups. The most important risk group is the hard drug using population (HDU) with an estimated prevalence of 60 to 80% among injecting drug users (IDU) and 2 to 35% in non-IDU.[11,12] Other risk groups for HCV infection in the Western world are those who received blood-products before 1991, first generation immigrants from endemic countries and travellers who had their skin pierced in non-Western countries.[1,13,14] Finally, HIV-positive men who have sex with men, family members of HCV infected persons and those with occupational risks of blood contact are also considered at risk.[15,16]

Success rates for HCV treatment have improved rapidly in the past years. At present, 50% of those infected with HCV genotype 1 and 4 and 80% of those with genotype 2 or 3 can be cured.[17] Increased treatment success rates have changed the perspective of HCV infection into that of a curable disease. This urges early detection to improve, but to date case finding of HCV remains a serious challenge for health care authorities and the need for new strategies is pressing.[18,19] Increasing the awareness of HCV among risk groups in the population and medical professionals is considered essential in these strategies. To improve HCV case finding in the Netherlands, the Ministry of Health initiated a national HCV campaign. This campaign consisted of two interventions, one aimed at the general population and medical professionals and one aimed at HDU in addiction care. The final design of the campaign was based on the evaluation of several regional pilot-campaigns.[20-22] We report the effectiveness and cost-effectiveness of this nationwide campaign aimed at improving case finding of HCV in the Netherlands.

Methods

Design

The nationwide campaign was targeted at all HCV risk groups and at primary care, public health and addiction care professionals in the Netherlands. It was implemented in 2009/2010 and comprised two large-scale interventions. The 'public intervention' focussed on risk groups in the general population and on medical professionals. The 'hard drug users intervention' (HDU-intervention) was specifically aimed at both injecting (IDU) and non-injecting drug users (non-IDU) in the addiction care setting.

Public intervention

The 'public intervention' was implemented in the six largest cities of the Netherlands; Amsterdam, Rotterdam, The Hague, Utrecht, Eindhoven and Almere, between September 2009 and February 2010. The intervention employed a funnelling approach based on the following steps:

1. The first step was increasing awareness. General information about HCV, its risk groups and treatment possibilities was spread through mass media such as radio advertisements, websites and internet banners. Brochures and posters were made available through GP practices, social services and pharmacies. Informative meetings were organized at venues where high risk groups were expected to congregate such as religious venues and cultural meetings.
2. The second step was to provide follow-up information for those who considered themselves at risk. A website providing a HCV-risk screening tool and elaborate information on risk groups, treatment possibilities, diagnostics and prognosis of HCV was available in several languages (www.hebikhepatitis.nl).
3. The third step focussed on training professionals. Public health service (GGD) employees were trained on the approach of immigrant populations. GP practice staff was systematically trained by regional GP support organisations, through group meetings and individual education. Educational material on HCV was developed and spread among all GP practices by the Dutch college of General Practitioners (NHG).
4. In the final step of the funnelling strategy, those who found themselves at increased risk consulted the GP or the regional public health service and were tested for HCV and if positive, referred for treatment.

Hard drug users intervention

The 'HDU-intervention', targeting both injecting and non-injecting drug users, was implemented in all 11 addiction care organisations of the Netherlands. The intervention ran from September 2009 to May 2011. In the methadone clinics and homeless shelters

associated with these organisations local coordinators were appointed and brochures and posters were distributed. The attending HDU were pro-actively approached by the addiction care workers and offered HCV related consultation and testing. In addition, group meetings were organized addressing the risks and treatment possibilities for HCV. Educational materials and symposia for professionals were provided to support the intervention. Testing was provided on the spot if possible or by referral to a regional laboratory where necessary.

Outcome

The primary aim of the nationwide HCV campaign was to increase the number of HCV carriers identified. The change in number of anti-HCV tests performed was used as the primary outcome to assess the effectiveness of the campaign. Cost-effectiveness, the secondary outcome of this evaluation, is expressed as cost per quality adjusted life year (QALY) in an incremental cost-effectiveness ratio (ICER).

Data collection

The anti-HCV test is used for primary identification of those ever infected with HCV. In case this test is positive, a HCV-RNA test is performed to test for chronic infection. Since the HCV-RNA test is also used for additional purposes, such as genotyping and assessment of the effect of treatment, the change in the number of anti-HCV tests performed was considered as the most reliable parameter of the campaign effect.

Collection of test-data was performed separately for the two interventions. To assess the change in the number of anti-HCV test resulting from the 'public intervention', data were collected from all 25 laboratories managing the diagnostic testing for the six large cities of the Netherlands. Data were collected from three time periods; the intervention period (September 2009 to February 2010) and from the same 6 months in the two preceding years. The number of tests during the six month intervention period was compared to the mean number of tests per six months, performed from September to February in the two preceding years. To correct for changes in the number of anti-HCV test not related to the 'public intervention', similar data from four large laboratories outside the 'public intervention' area (Groningen, Tilburg, Nijmegen and Breda) were collected. Anti-HCV tests performed in addiction care were not included in this data collection.

For the 'HDU-intervention' the number of HCV related consultations, anti-HCV tests and positive tests performed were registered in the addiction care centres. These data were linked to anonymous HCV carrier characteristics such as age, genotype and relevant comorbidity. Registration was performed by the Netherlands Institute of Mental Health and Addiction ('Trimbos' institute) using standardized procedures. The number and result of HCV tests performed during the intervention were extracted from

this registration by one of the researchers. Because the 'HDU-intervention' was implemented in all the addiction care institutions in the Netherlands, there was no control region available. The number of HCV tests performed in routine addiction care before the intervention was used for control comparison.[22]

Costs

The additional costs resulting from the nationwide hepatitis C campaign were estimated based on direct, indirect and prevented costs.

The direct and indirect costs were registered by all participating organizations in both interventions using standardized forms. Processing of these cost-data by the researchers was done in personal contact with the participating and coordinating institutions. Direct costs result from the implementation of the interventions, such as costs of meetings, training, materials and media used. Indirect costs result from the consequences of the interventions, such as time spent on consultations, testing, guidance during treatment and education (course of events depicted in figure 1).

Prevented costs are medical costs prevented by early identification and treatment of HCV carriers, such as costs related to the treatment of end-stage liver disease (e.g. cirrhosis and cancer). These costs were calculated based on the Markov model (see below).[20,23]

Analyses

The incremental effect of the 'public intervention' was analysed using a Bayesian Poisson model. This model calculates the incremental campaign effect in the intervention regions based on the data observed in both the intervention and control regions.

Since there was no control region available for the 'HDU-intervention', calculations based on a Bayesian Poisson model were not applicable. In stead, the point estimate from the aforementioned registration was used. To quantify the potential effect of overestimation resulting from the lack of a control region, additional sensitivity (scenario) analyses were performed to test the effect of different levels of overestimation on cost-effectiveness.

Cost-effectiveness

The ICER is the ratio of the additional effects, expressed in quality adjusted life years (QALYs) and costs brought about by an intervention such as the HCV campaign.[24] The ICER provides an objective outcome that can be used to quantify the cost-effectiveness of an intervention and was calculated separately for both interventions. To calculate the ICERs and the prevented costs, a Markov model was used that was updated for 2011 and supplemented with information from the registrations performed for both interventions.[20,23]

Sensitivity and uncertainty analyses

The ICER is influenced by the parameters that are used in the model. This pertains to all input parameters such as percentages of carriers receiving diagnostics and treatment, but also carrier characteristics and prevalence rates.

To evaluate which of these parameters are of largest impact on the ICER multivariate sensitivity analyses were performed for the ICERs of both interventions. These analyses provide information concerning the models' sensitivity to uncertainty in the individual model parameters, but also on the influence of possible interactions between parameters. The multivariate sensitivity outcome is expressed in standardized regression coefficients (SRCs) which represent the proportion of explained variance in the outcome. The SRCs are obtained from a probabilistic sensitivity analyses (PSA) using Monte Carlo simulations. Convergence of the results was obtained after 5,000 iterations for both interventions.

The simulated net costs, plotted against the corresponding gain in QALYs are demonstrated in a cost-effectiveness plane. The likelihood that the interventions are cost-effective at varying thresholds, are depicted in a cost-effectiveness acceptability curve.

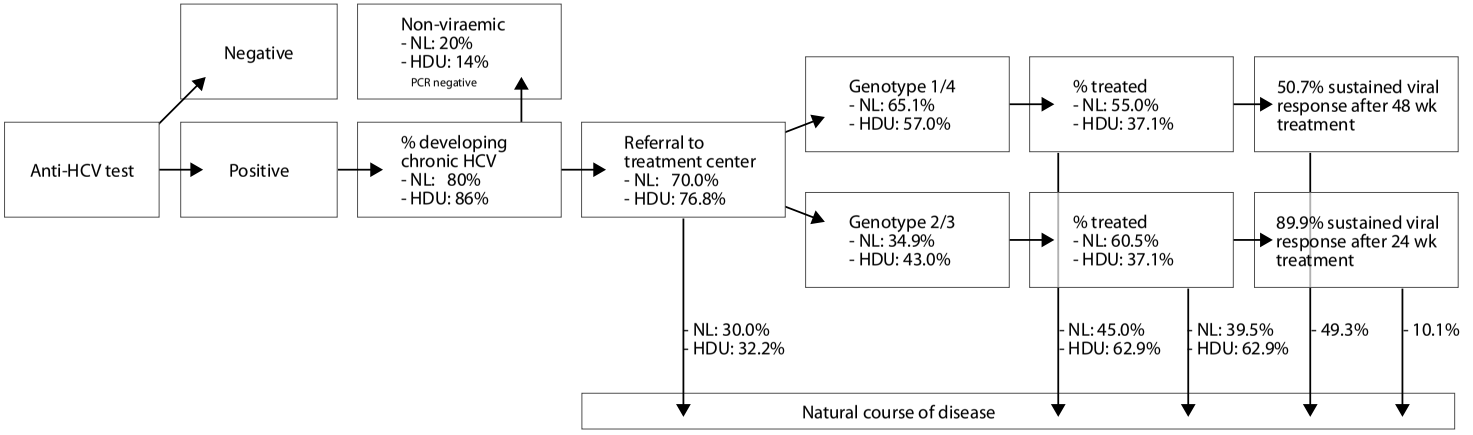
Results

The effects of both interventions are demonstrated in table 1. The costs of both interventions are demonstrated in table 2. The expected course of events was based on the observations in our registrations and previous studies and is depicted in figure 1.

Public intervention

Suitable data was obtained from 20 of the 25 laboratories in the intervention regions and from all contacted laboratories in the control regions. In the intervention regions, one laboratory performed only confirmation of tests found positive elsewhere and was excluded to avoid duplicate counting. Four laboratories could not deliver data because of restrictions due to logistic reasons, such as lack of personnel or financial resources. The number of missing tests from these centres was estimated based on the number of tests performed in laboratories which were similar in characteristics and catchment area. As a result the missing HCV data was estimated to be approximately 12.6% in the intervention period, and 13.3% in the data concerning preceding years. To correct for missing data these numbers were added to the number of tests performed in the intervention regions in the corresponding measurement periods.

Figure 1. Course of events after identification[3,22,40-42]



NL: General population, used for 'public intervention'. HDU: hard drug using population, used for 'HDU-intervention'.

Effects

In the 'public intervention' regions, the number of tests increased from a mean of 22,815 tests in the control period (i.e. September to February in the two preceding years) to 25,750 in the six-month intervention period, which is an increase of 12.9%. In the control regions the number of anti-HCV tests increased from a mean of 11,933 in the control period, to 12,655 tests during the intervention period (table 1). This is an increase of 6.1%. Consequently the net increase in the intervention period is 6.8% (95% CI 6.2-7.4%). This represents 1,554 HCV tests that were attributed to the HCV campaign. In the intervention regions the number of positive anti-HCV tests increased from a mean of 864 in the control period to 1,091 in the intervention period (26.3% increase). In the control regions this number increased from a mean of 280 in the control period to 337 tests in the intervention period (20.4% increase). The percentage of HCV positive tests increased from 3.8 to 4.2% in the intervention region and from 2.4 to 2.7% in the control region. The additional 5.9% increase (95% CI 0.4-11.5%) in positive tests the intervention regions represents 49 additional positive anti-HCV tests in the intervention period. The repeated calculation using the Bayesian Poisson model demonstrated a similar outcome at 47 positive tests. The latter indicates, since 80% of the anti-HCV positive tests is expected to lead to a chronic infection, that approximately 38 additional chronic HCV carriers have been identified by the 'public intervention'.[25,26] The data registration demonstrated that 65.1% of these carriers were infected with genotype 1 or 4 (the rest was genotype 2/3). These numbers were used to calculate the ICER.

Costs

Table 2 shows the direct and indirect costs including 95% confidence intervals. The direct costs of the implementation of the 'public intervention' were approximately 598,000 euro. The indirect costs were estimated at 318,500 euro. The total costs for the 'public intervention' were 916,500 euro. The estimated costs per identified HCV carrier were 24,450 euro.

Hard drug users intervention

Effects

Data were provided by all 11 addiction care centres. The number of HCV consultations registered during the intervention period in these centres was 1,810, resulting in 1,130 anti-HCV tests. The number of positive tests was 299 (26.5%). For HDU, the mean age at time of anti-HCV testing was 46.1 years of age. In the pilot campaign, the percentage of chronic infection among anti-HCV positives in the HDU population was 86%.[22] Using these data as a reference indicates that 257 (95% CI: 244 to 276) chronic HCV carriers were identified. Since HCV testing among HDU in addiction care in the Netherlands was

demonstrated to be very scarce before the intervention period, the identification of these 257 HCV carriers was considered as a direct consequence of the campaign.[22] Of the HDU tested positive, 57% was infected with genotype 1 or 4 and 33% with genotype 2 or 3. Registration data demonstrated that 76.8% of these carriers were referred to a treatment centre.

Table 1. Effects of the two interventions on number of tests and consultations

Anti-HCV tests, positive anti-HCV tests and consultations	
Public intervention	
Intervention regions - mean number of anti-HCV tests in control periods	22,815
Intervention regions - number of anti-HCV tests in intervention period	25,750 12.9% increase
Control regions - mean number of anti-HCV tests in control periods	11,933
Control regions - number of anti-HCV tests in intervention period	12,655 6.1% increase
Additional anti-HCV tests resulting from the intervention - corrected for increase in control region	1,554
Intervention regions - mean number of positive anti-HCV tests in control periods	864
Intervention regions - number of positive anti-HCV tests in intervention period	1,091 26.3% increase
Control regions - mean number of positive anti-HCV tests in control periods	280
Control regions - number of positive anti-HCV tests in intervention period	337 20.4% increase
Additional positive anti-HCV tests resulting from the intervention	
- calculated based on the before mentioned increase in tests	49
- calculated based on Bayesian Poisson model – used in Markov model	47
Additionally identified HCV carriers resulting from the intervention	
- 80% of positive tests as calculated by the Bayesian Poisson model	38
Hard drug users intervention	
Additional HCV related consultations resulting from the intervention	1,810
Additional anti-HCV tests resulting from the intervention	1,130
Additional positive anti-HCV tests resulting from the intervention	299
Additional identifications of chronic HCV resulting from the intervention - 86% of positive tests	257

Table 2. Direct and indirect costs of the two interventions

Costs	Costs in € (95% CI)
Public intervention	
Direct costs, resulting from organisation, campaign execution and materials	598,408 (556,199 – 640,775)
Indirect costs, resulting from additional consultations, testing and treatment	318,429 (69,036 –1,233,597)
Total costs of the 'public intervention'	*916,837 (638,008 – 1,835,889)*
Hard drug users intervention	
Direct costs, resulting from organisation, campaign execution and materials	346,561 (321,870 – 371,074)
Indirect costs, resulting from additional consultations, testing and treatment	1,741,024 (1,349,488 – 2,158,108)
Total costs of the 'HDU-intervention'	*2,087,585 (1,696,178 – 2,507,852)*

Costs

Table 2 shows the direct and indirect costs including 95% confidence intervals. The direct costs of the 'HDU-intervention' were approximately 346,500 euro and the indirect costs were about 1,741,000 euro. Consequently, the total cost were of approximately 2,087,500 euro leading to an estimated cost of 8,120 euro (95%CI: € 6,780 - € 9,547) per identified chronic HCV carrier.

Cost-effectiveness

For the 'public intervention', the Markov model calculated discounted incremental cost of 591 euro (95%CI: € 408 - € 1,178) per tested person with an associated gain of 0.035 QALYs (95%CI: 0.000 - 0.167). Consequently, the ICER is 16,673 euro (95%CI: € 6,774 - € 21,907,423) per QALY.

The 'HDU-intervention' yielded discounted incremental cost of 1,847 euro (95%CI: € 1,490 - € 2,237) per tested person with an associated gain of 0.22 QALYs (95%CI: 0.15 - 0.32). As a result, the ICER of the 'HDU-intervention' is 8,245 euro per QALY (95%CI: € 6,109 - € 11,349 euro).

Uncertainty and sensitivity analyses

The cost-effectiveness plane and the cost-effectiveness acceptability curve are provided as figure 2 and 3.

Figure 2. Cost-effectiveness plane - simulated net costs and corresponding gain in QALYs

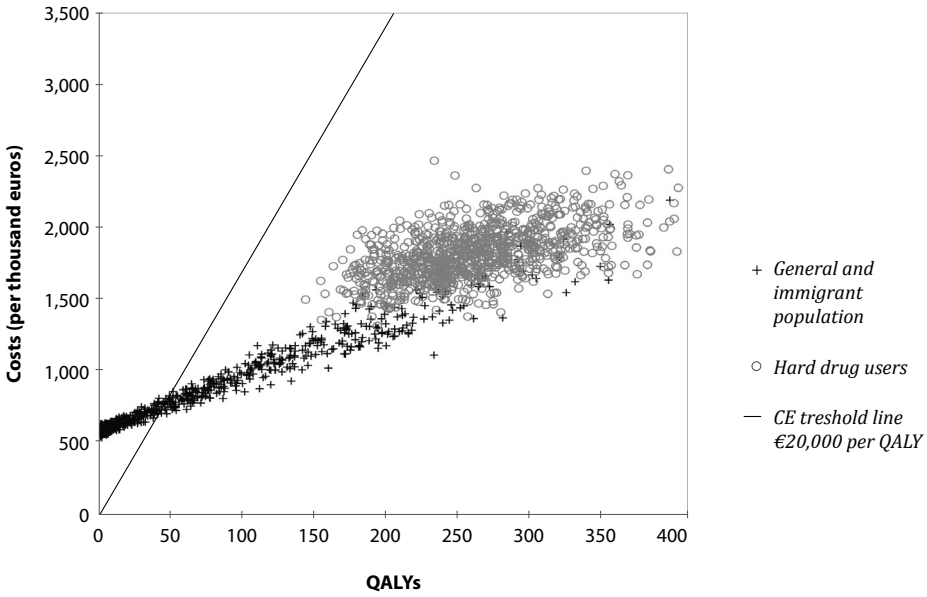
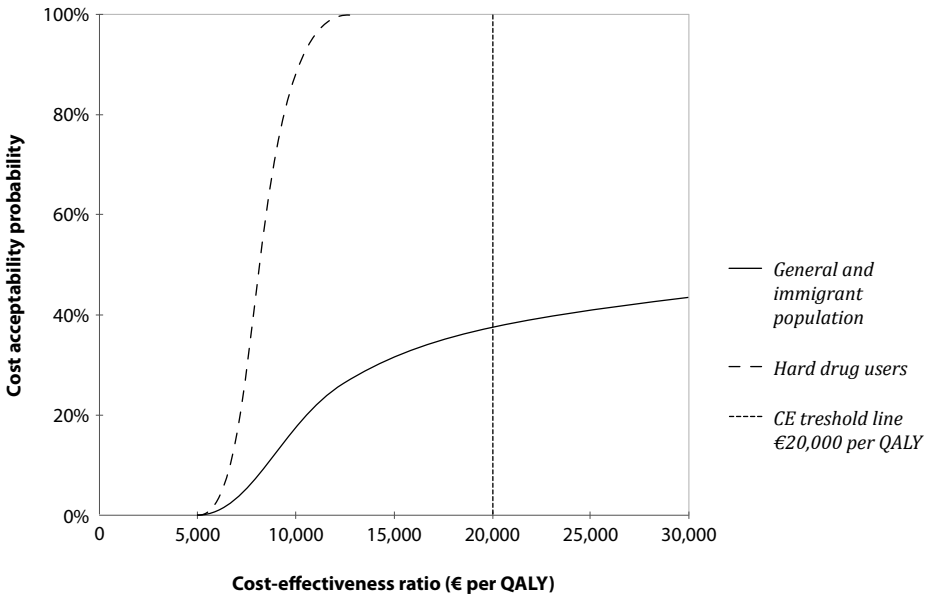


Figure 3. Cost-effectiveness acceptability curve - probability that the interventions are cost-effective at varying thresholds of societal willingness to pay for an additional QALY



In the Netherlands, a threshold of 20,000 euro is generally used as a cut-off point for cost-effectiveness.[27] The uncertainty analysis demonstrates that the likelihood that the ICER of the 'public intervention' remains below this threshold is 37%. For the 'HDU-intervention', the maximum estimated ICER is 15,008 euro. Therefore, the chance that the ICER will exceed 20,000 euro threshold is negligible.
The multivariate sensitivity analysis demonstrates that the ICER for the 'public intervention' is primarily sensitive to changes in the number of identified HCV carriers (SRC -99%). For the health gain (and consequently for the ICER), the second most influential parameter is the referral rate with an SRC of 7.1% (SRC for the ICER: -5%). For the costs, the second most influential parameter were the direct intervention costs at an SRC of 6.7%. The total variance explained (R^2) by the regression model that was fitted for these sensitivity analyses was 98% or more.
For the 'HDU-intervention', the ICER is primarily sensitive to changes in the percentage of carriers that wants to be treated. The corresponding SRCs are -64% for carriers with genotype 2/3 and -29% for carriers with genotype 1/4. The ICER is also influenced by the costs of treatment of cirrhosis (SRC 30%), the referral rate (SRC -22%), the genotype distribution (SRC based on genotype 2/3 is -22%) and the chance of transition from mild to moderate hepatitis (SRC -21%). The R^2 values for these sensitivity analyses were 95% or more.
The lack of a control region for the 'HDU-intervention' could have led to an overestimation of the effect. The additional sensitivity analyses performed quantify the potential effect of such overestimation, demonstrated that a reduction of the effect by 50% would result in an ICER of approximately 10,000 euro. The threshold of 20,000 euro was reached at a reduction in effect of 85%. This indicates that if an overestimation of the effect occurred, it is not likely to have influenced the resulting ICER substantially.

Discussion

Summary of findings

The nationwide hepatitis C campaign in the Netherlands resulted in an increase in the number of HCV tests performed, both in the 'public intervention' as well as the intervention targeting hard drug users. The number of HCV carriers identified increased as well, resulting in a net increase of 295 carriers diagnosed with HCV as a result of the campaign. The estimated ICER of the 'public intervention' is 16,673 euro. However, the probability that the ICER remains below the Dutch threshold for cost-effectiveness of 20.000 euro in a similar situation is only 37%. The estimated ICER for the 'hard drug users intervention' is 8,245 euro with a maximum estimated ICER of 15,000 Euro. This indicates that the intervention targeted at HDU was cost-effective.

The cost-effectiveness analyses of the pilot-campaigns, evaluating comparable interventions on a smaller scale, found an ICER of 11,297 for a strategy comparable to the 'public intervention' and an ICER of 7,321 for a comparable 'HDU intervention'.[20] Particularly the result of the pilot campaign targeting the general population was more favourable. The relatively modest effect for the current 'public intervention' can, at least partially, be explained by the co-occurrence of the H1N1 influenza virus pandemic during the intervention period in 2009. The H1N1-pandemic emerged in the Netherlands one month after the start of the nationwide hepatitis C campaign. It dominated the media and caused heavy workload for general practitioners due to increased GP consultations and the vaccination of risk groups. The resulting reduction in attention and involvement of GPs and risk groups may have reduced the effectiveness of the 'public intervention' considerably.[21]

Accepted cost-effectiveness thresholds differ substantially per country.[28] In the Netherlands, this threshold is relatively low.[27] However, the maximum value for the ICER for the 'public intervention' vastly exceeds the maximum value of all international thresholds. Therefore, the uncertainty concerning the cost-effectiveness of this intervention remains at all international perspectives.

Strengths and limitations

The main strength of this study is that it is based on the evaluation of a 'real-life' nationwide hepatitis C campaign implementing large scale interventions. This study therefore provides a realistic rather than a theoretical estimation of the effects and cost-effectiveness of nationwide interventions.

Interpretation of the results is limited by the imperfections in the dataset, such as missing data, the lack of a proper control region for the intervention aimed at HDU and possible flaws in the registrations. This may have caused uncertainty in the effect estimations, which we tried to counter by the uncertainty analysis. There was no reason to expect differences in the nature of missing data and possible flaws in the registrations for the intervention and control regions of the 'public intervention'. Therefore, this is not expected to have substantially affected the estimations of the effect. The lack of a control region for the 'HDU-intervention' could have led to an overestimation of the effect. However, the pilot campaign indicated that HCV case finding in routine addiction care was rare before the intervention. Therefore, the HCV tests performed during the intervention could all be considered as a direct consequence of the 'HDU-intervention'.[22] In addition, the sensitivity analysis demonstrated that the threshold for cost-effectiveness would only be exceeded if the effect is overestimated by 85%. Therefore, it is very unlikely that a potential overestimation of the effectiveness of the HDU campaign has substantially influenced the estimated cost-effectiveness of this intervention.

The measurements of the campaign effect were limited to the active intervention periods for both interventions. Long-term effects of the campaign could not be included in the analyses. Considering the attention paid to implementation in case finding protocols and the increased awareness induced among medical professionals and risk groups, it is likely that longer follow up would lead to a more favourable ICER due to an increase in campaign effect.[29]

A qualitative evaluation by the 'Trimbos' institute describes additional health improvements resulting from the 'HDU-intervention'.[30] Life-style improvements are seen in consulting HDU as a consequence of increased awareness of the dangers of a lack of hygiene and risk behaviour. This effect is even larger in HCV infected HDU who undergo HCV-treatment.[30] Consequently, improved overall health resulting in an increase of quality of life and possibly a reduction of future medical costs would lead to a more favourable ICER.

Future developments

Several developments are expected to improve cost-effectiveness in the near future.[20] More effective and shorter HCV treatment regimens and earlier recognition of treatment failure, will increase health gain and reduce treatment burden and costs.[17,20,31,32]

In addition, the number of immigrants in the Netherlands is expected to keep growing and the definition of those at risk is expected to improve.[14,33] An increase in the population at risk and detailing of the risk groups in need of screening are likely to improve cost-effectiveness.

On the other hand, injecting drug use is gradually losing popularity and public health interventions have reduced HCV transmission rates among HDU.[34-36] In addition, the implementation of HCV screening in protocols for HDU is expected to be most effective in the first phase, because of the initial 'catch-up' in identification of HCV carriers susceptible to this strategy. In the longer term, the effect of the 'HDU-intervention' strategy is expected to diminish.

Finally, given the overlap in modes of transmission and risk groups, a combined approach with HBV, HIV and HCV should be considered in future campaigns. A combined campaign is likely to increase participation by risk groups and health care professionals.

Comparison to literature

A recent review on the cost-effectiveness of hepatitis C screening demonstrates that HCV screening is likely to be cost-effective in populations with relatively high prevalence, whereas cost-effective screening in populations with lower prevalences is hard to attain.[18] This is consistent with the finding in our study that only the intervention aimed at the group with the highest risk is clearly cost-effective. However, in most earlier studies the uncertainty surrounding the cost-effectiveness is considerable.[18,37-40]

The comparatively positive outcome in our study is likely to be due to the relatively low costs and high gain in effect. In part, this can be explained by the high acceptance rate for testing in our study. Castelnuevo et al. found an acceptance rate among HDU of 49% for anti-HCV testing. Of those tested positive only 39% underwent the necessary PCR testing. In our study the acceptance rate among HDU was 62% and PCR was generally performed automatically if the anti-HCV test was positive.[39] This difference may be explained by the fact that addiction care in the Netherlands is well organized, with close monitoring and regular contact with the majority of the HDU.

Conclusion

In a national campaign aimed at increasing awareness and improving case finding of hepatitis C, the intervention aimed at hard drug users was shown to be cost-effective. The intervention aimed at the general population only marginally increased the number of HCV carriers diagnosed and leaves cost-effectiveness undetermined. The results of our study demonstrate that HCV campaigns aimed at the general public alone will not adequately improve case finding of HCV. Therefore, new strategies for case finding of hepatitis C need to be developed, focussing on high risk groups in the population.

Acknowledgements
This evaluation of the nationwide HCV campaign was funded by the Netherlands Organisation for Health Research and Development (ZonMw). The cooperation of the Netherlands Institute of Mental Health and Addiction 'Trimbos', the laboratories providing the test data and the cooperation of the addiction care institutions was vital to this evaluation. A list of these institutions is provided as supplementary information. Conflicts of interest: Neither the lead author nor any of the co-authors report any conflict of interests.

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FAST eerste lijn, Eindhoven
Flevo ziekenhuis, Almere
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GG&GD Utrecht
GGD Almere
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GGD Rotterdam-Rijnmond
Havenziekenhuis, Rotterdam
IrisZorg
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Rijnstate ziekenhuis, Arnhem
ROSA, Almere
Saltro Diagnostisch Centrum, Utrecht
SHO Medisch Diagnostisch Centrum
St Fransciscus Gasthuis, Rotterdam
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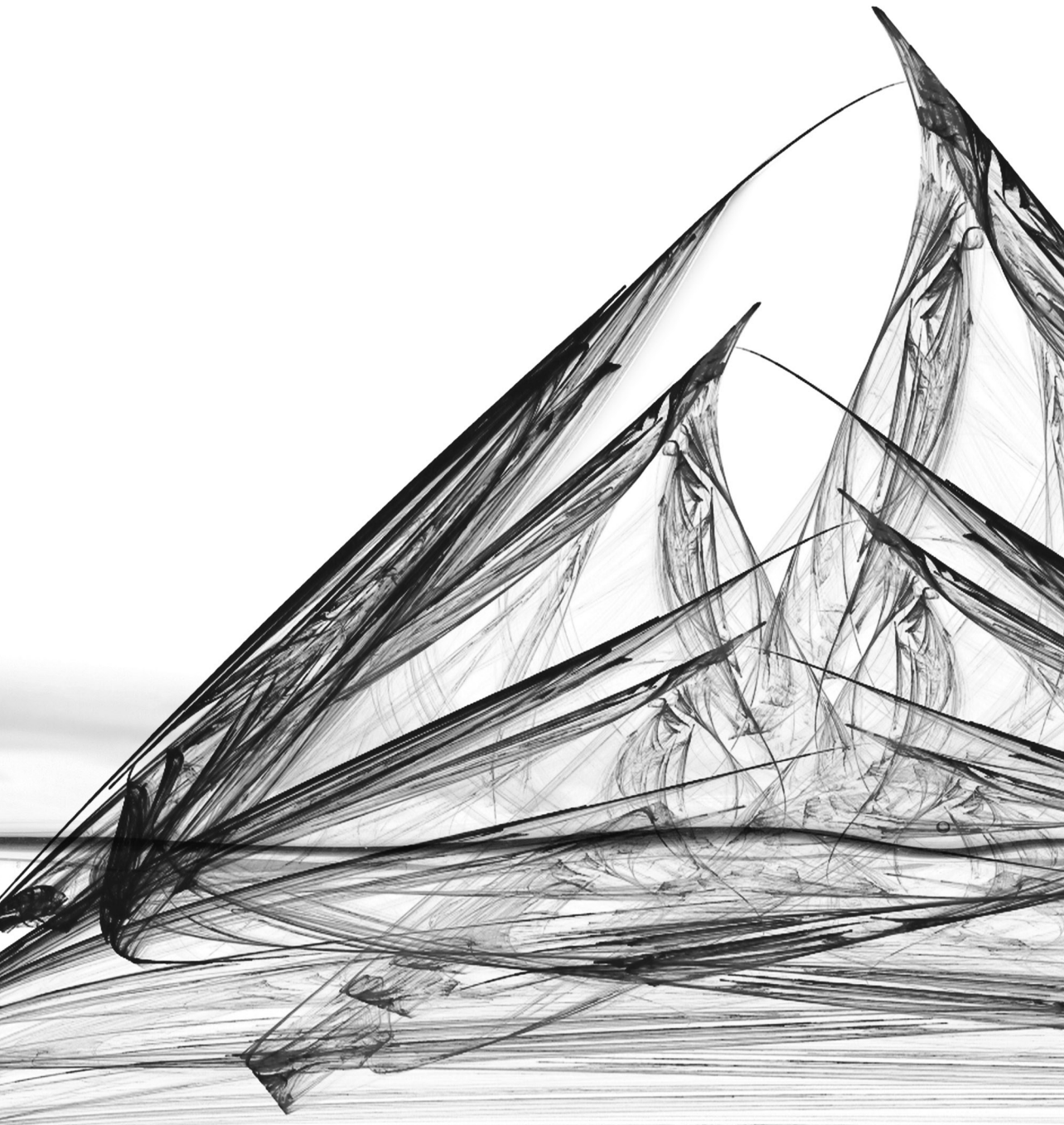
Reference List

1. Hepatitis C: global prevalence. Wkly Epidemiol Rec 1997; 72(46):341-344.
2. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis 2005; 5(9):558-567.
3. Lauer GM, Walker BD. Hepatitis C virus infection. N Engl J Med 2001; 345(1):41-52.
4. World Health Organization (WHO). State of the art of vaccine research and development. Report number WHO/IVB/05.XX. 2011.
5. Cornberg M, Razavi HA, Alberti A, Bernasconi E, Buti M, Cooper C et al. A systematic review of hepatitis C virus epidemiology in Europe, Canada and Israel. Liver Int 2011; 31 Suppl 2:30-60.
6. Slavenburg S, Verduyn-Lunel FM, Hermsen JT, Melchers WJ, te Morsche RH, Drenth JP. Prevalence of hepatitis C in the general population in the Netherlands. Neth J Med 2008; 66(1):13-17.
7. Baaten GG, Sonder GJ, Dukers NH, Coutinho RA, van den Hoek JA. Population-based study on the seroprevalence of hepatitis A, B, and C virus infection in Amsterdam, 2004. J Med Virol 2007; 79(12):1802-1810.
8. Kretzschmar MEE. The prevalence of hepatitis C in the Netherlands - Report for ministry of Welfare and Sports [in Dutch: De prevalentie van hepatitis C in Nederland]. notitie RIVM . 2-12-2004.
9. Kok A, Zuure FR, Weegink CJ, Coutinho RA, Prins M. [Hepatitis C in the Netherlands: sparse data on the current prevalence and the necessity for epidemiological studies and innovative methods for detecting infected individuals]. Ned Tijdschr Geneeskd 2007; 151(43):2367-2371.
10. Health Council of the Netherlands: Committee on hepatitis C. Detection and treatment of people with hepatitis C. 1997/19. 1997. Rijswijk.
11. Scheinmann R, Hagan H, Lelutiu-Weinberger C, Stern R, Des J, Flom PL et al. Non-injection drug use and Hepatitis C Virus: a systematic review. Drug Alcohol Depend 2007; 89(1):1-12.
12. Nelson PK, Mathers BM, Cowie B, Hagan H, Des JD, Horyniak D et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. Lancet 2011.
13. van de Laar TJ, Koppelman MH, van der Bij AK, Zaaijer HL, Cuijpers HT, van der Poel CL et al. Diversity and origin of hepatitis C virus infection among unpaid blood donors in the Netherlands. Transfusion 2006; 46(10):1719-1728.
14. Urbanus AT, van de Laar TJ, van den HA, Zuure FR, Speksnijder AG, Baaten GG et al. Hepatitis C in the general population of various ethnic origins living in the Netherlands: should non-Western migrants be screened? J Hepatol 2011.
15. Clarke A, Kulasegaram R. Hepatitis C transmission -- where are we now? Int J STD AIDS 2006; 17(2):74-80.
16. de Vries MJ, te RB, van Nieuwkerk CM. Transmission of hepatitis C genotypes in the Netherlands amongst recently genotyped patients. Neth J Med 2008; 66(1):40-41.
17. Manns MP, Foster GR, Rockstroh JK, Zeuzem S, Zoulim F, Houghton M. The way forward in HCV treatment--finding the right path. Nat Rev Drug Discov 2007; 6(12):991-1000.
18. Sroczynski G, Esteban E, Conrads-Frank A, Schwarzer R, Muhlberger N, Wright D et al. Long-term effectiveness and cost-effectiveness of screening for hepatitis C virus infection. Eur J Public Health 2009; 19(3):245-253.
19. Gravitz L. a smouldering public-health crisis. Nature 2011; 474(7350):S2-S4.
20. Helsper C.W., Borkent-Raven B.A., de Wit N.J., van Essen G.A., Bonten M.J.M., Janssen M.P. et al. Cost-effectiveness of targeted screening for hepatitis C in the Netherlands. Infection and Epidemiology 2010.
21. Helsper CW, van Essen GA, Bonten MJ, de Wit NJ. A support programme for primary care leads to substantial improvements in the effectiveness of a public hepatitis C campaign. Fam Pract 2010; 27(3):328-332.

22. Veen van der C , Hoogenboezem G, Breemer J. Education campaign for hepatitis C aimed at hard drug users. Results of a pilot study [in Dutch: Voorlichtingscampagne rond hepatitis C gericht op drugsgebruikers. Resultaten van een pilotstudie]. Verslaving: tijdschrift over verslavingsproblematiek 2009; 5(2):61-71.
23. Siebert U, Sroczynski G, Rossol S, Wasem J, Ravens-Sieberer U, Kurth BM et al. Cost effectiveness of peginterferon alpha-2b plus ribavirin versus interferon alpha-2b plus ribavirin for initial treatment of chronic hepatitis C. Gut 2003; 52(3):425-432.
24. Meltzer MI. Introduction to health economics for physicians. Lancet 2001; 358(9286):993-998.
25. Alter MJ, Kruszon-Moran D, Nainan OV, McQuillan GM, Gao F, Moyer LA et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N Engl J Med 1999; 341(8):556-562.
26. Conry-Cantilena C, VanRaden M, Gibble J, Melpolder J, Shakil AO, Viladomiu L et al. Routes of infection, viremia, and liver disease in blood donors found to have hepatitis C virus infection. N Engl J Med 1996; 334(26):1691-1696.
27. Berg van den M, de Wit GA, Vijgen SM, Busch MC, Schuit AJ. Cost-effectiveness of prevention: opportunities for public health policy in the Netherlands. Ned Tijdschr Geneeskd 2008; 152(23):1329-1334.
28. World Health Organization (WHO). Table: Threshold values for intervention cost-effectiveness by Region. 2005.
29. E.Croes, C.van der Veen, (Trimbos instituut). Factors influencing the implementation of a hepatitis C campaign for hard drug users [in Dutch: Beinvloedende factoren bij de implementatie van de hepatitis C informatiecampagne voor drugsgebruikers]. 2011.
30. de Jong I, Dijkstra M, van der Poel A, (the Netherlands Institute of Mental Health and Addiction 'Trimbos'). Care for hard drug users after treatment for hepatitis C [in Dutch 'Nazorg voor harddrugsgebruikers na behandeling van hepatitis C']. 978-90-5253-666-8. 2011.
31. Zeuzem S. Interferon-based therapy for chronic hepatitis C: current and future perspectives. Nat Clin Pract Gastroenterol Hepatol 2008; 5(11):610-622.
32. Soriano V, Peters MG, Zeuzem S. New therapies for hepatitis C virus infection. Clin Infect Dis 2009; 48(3):313-320.
33. Statistics Netherlands (CBS). Population forecast 2010 to 2060: assumptions on immigration [in Dtuch: Bevolkingsprognose 2010-2060: veronderstellingen over immigratie]. 42-50. 1-12-2010.
34. van den Berg CH, Smit C, Bakker M, Geskus RB, Berkhout B, Jurriaans S et al. Major decline of hepatitis C virus incidence rate over two decades in a cohort of drug users. Eur J Epidemiol 2007; 22(3):183-193.
35. van den BC, Smit C, Van BG, Coutinho R, Prins M. Full participation in harm reduction programmes is associated with decreased risk for human immunodeficiency virus and hepatitis C virus: evidence from the Amsterdam Cohort Studies among drug users. Addiction 2007; 102(9):1454-1462.
36. van de Laar TJ, Langendam MW, Bruisten SM, Welp EA, Verhaest I, van Ameijden EJ et al. Changes in risk behavior and dynamics of hepatitis C virus infections among young drug users in Amsterdam, the Netherlands. J Med Virol 2005; 77(4):509-518.
37. Sutton AJ, Edmunds WJ, Sweeting MJ, Gill ON. The cost-effectiveness of screening and treatment for hepatitis C in prisons in England and Wales: a cost-utility analysis. J Viral Hepat 2008; 15(11):797-808.
38. Leal P, Stein K, Rosenberg W. What is the cost utility of screening for hepatitis C virus (HCV) in intravenous drug users? J Med Screen 1999; 6(3):124-131.
39. Castelnuovo E, Thompson-Coon J, Pitt M, Cramp M, Siebert U, Price A et al. The cost-effectiveness of testing for hepatitis C in former injecting drug users. Health Technol Assess 2006; 10(32):iii-xii, 1.
40. Thompson-Coon J., Castelnuovo E, Pitt M, Cramp M, Siebert U, Stein K. Case finding for hepatitis C in primary care: a cost utility analysis. Fam Pract 2006; 23(4):393-406.

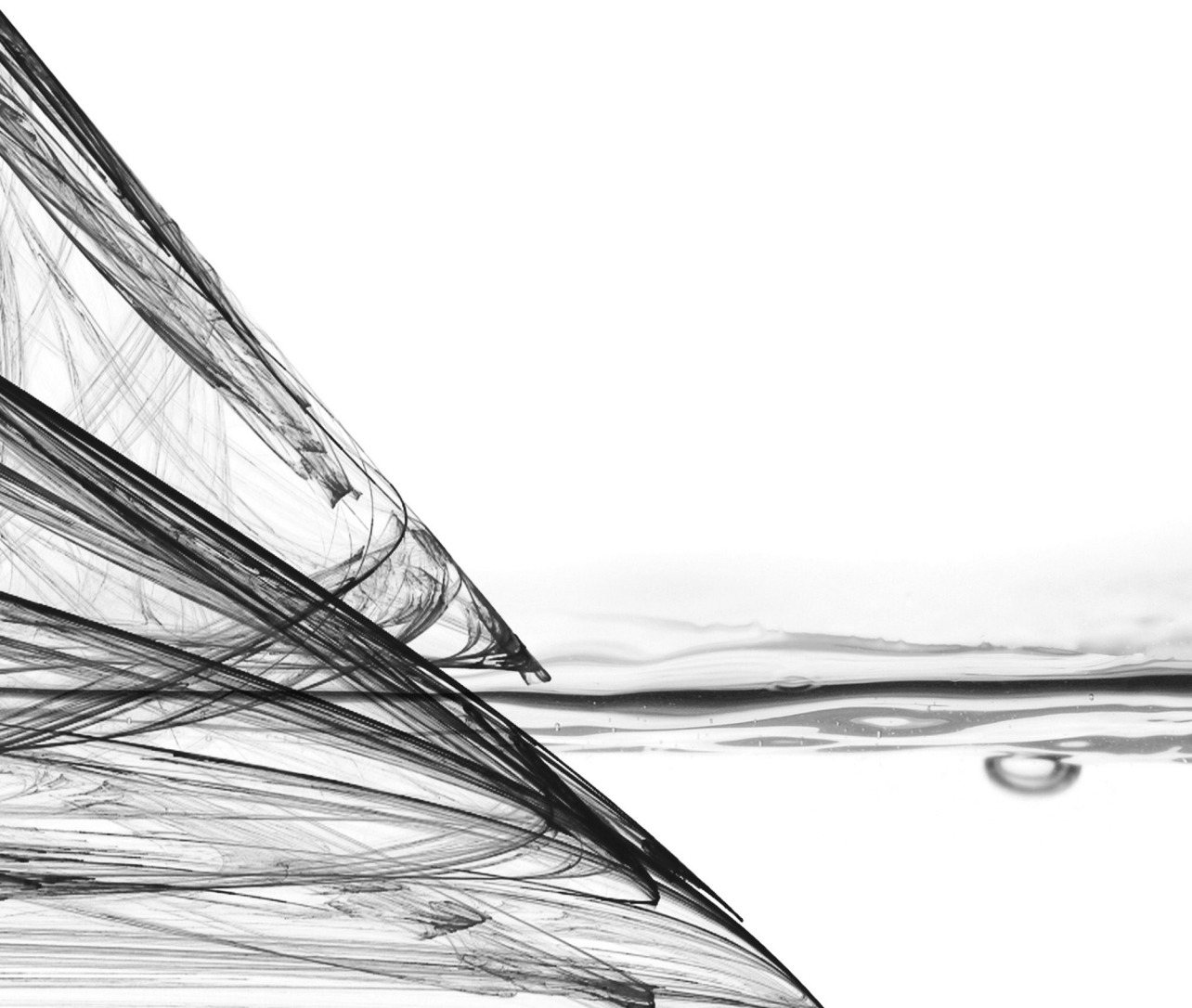
41. Foster GR, Goldin RD, Main J, Murray-Lyon I, Hargreaves S, Thomas HC. Management of chronic hepatitis C: clinical audit of biopsy based management algorithm. BMJ 1997; 315(7106):453-458.
42. de Jong DJ, de Vries MJ, Boonman-de Winter LJ, van WP. Referral of hepatitis C virus seropositive patients in primary care in the Netherlands. Neth J Med 2008; 66(1):42-43.
43. drug users. Results of a pilot study [in Dutch: Voorlichtingscampagne rond hepatitis C gericht op drugsgebruikers. Resultaten van een pilotstudie]. Verslaving: tijdschrift over verslavingsproblematiek 2009; 5(2):61-71.
44. Siebert U, Sroczynski G, Rossol S, Wasem J, Ravens-Sieberer U, Kurth BM et al. Cost effectiveness of peginterferon alpha-2b plus ribavirin versus interferon alpha-2b plus ribavirin for initial treatment of chronic hepatitis C. Gut 2003; 52(3):425-432.
45. Meltzer MI. Introduction to health economics for physicians. Lancet 2001; 358(9286):993-998.
46. Alter MJ, Kruszon-Moran D, Nainan OV, McQuillan GM, Gao F, Moyer LA et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N Engl J Med 1999; 341(8):556-562.
47. Conry-Cantilena C, VanRaden M, Gibble J, Melpolder J, Shakil AO, Viladomiu L et al. Routes of infection, viremia, and liver disease in blood donors found to have hepatitis C virus infection. N Engl J Med 1996; 334(26):1691-1696.
48. Berg van den M, de Wit GA, Vijgen SM, Busch MC, Schuit AJ. Cost-effectiveness of prevention: opportunities for public health policy in the Netherlands. Ned Tijdschr Geneeskd 2008; 152(23):1329-1334.
49. World Health Organization (WHO). Table: Threshold values for intervention cost-effectiveness by Region. 2005.
50. E.Croes, C.van der Veen, (Trimbos instituut). Factors influencing the implementation of a hepatitis C campaign for hard drug users [in Dutch: Beinvloedende factoren bij de implementatie van de hepatitis C informatiecampagne voor drugsgebruikers]. 2011.
51. de Jong I, Dijkstra M, van der Poel A, (the Netherlands Institute of Mental Health and Addiction 'Trimbos'). Care for hard drug users after treatment for hepatitis C [in Dutch 'Nazorg voor harddrugsgebruikers na behandeling van hepatitis C']. 978-90-5253-666-8. 2011.
52. Zeuzem S. Interferon-based therapy for chronic hepatitis C: current and future perspectives. Nat Clin Pract Gastroenterol Hepatol 2008; 5(11):610-622.
53. Soriano V, Peters MG, Zeuzem S. New therapies for hepatitis C virus infection. Clin Infect Dis 2009; 48(3):313-320.
54. Statistics Netherlands (CBS). Population forecast 2010 to 2060: assumptions on immigration [in Dtuch: Bevolkingsprognose 2010-2060: veronderstellingen over immigratie]. 42-50. 1-12-2010.
55. van den Berg CH, Smit C, Bakker M, Geskus RB, Berkhout B, Jurriaans S et al. Major decline of hepatitis C virus incidence rate over two decades in a cohort of drug users. Eur J Epidemiol 2007; 22(3):183-193.
56. van den BC, Smit C, Van BG, Coutinho R, Prins M. Full participation in harm reduction programmes is associated with decreased risk for human immunodeficiency virus and hepatitis C virus: evidence from the Amsterdam Cohort Studies among drug users. Addiction 2007; 102(9):1454-1462.
57. van de Laar TJ, Langendam MW, Bruisten SM, Welp EA, Verhaest I, van Ameijden EJ et al. Changes in risk behavior and dynamics of hepatitis C virus infections among young drug users in Amsterdam, the Netherlands. J Med Virol 2005; 77(4):509-518.
58. Sutton AJ, Edmunds WJ, Sweeting MJ, Gill ON. The cost-effectiveness of screening and treatment for hepatitis C in prisons in England and Wales: a cost-utility analysis. J Viral Hepat 2008; 15(11):797-808.
59. Leal P, Stein K, Rosenberg W. What is the cost utility of screening for hepatitis C virus (HCV) in intravenous drug users? J Med Screen 1999; 6(3):124-131.

60. Castelnuovo E, Thompson-Coon J, Pitt M, Cramp M, Siebert U, Price A et al. The cost-effectiveness of testing for hepatitis C in former injecting drug users. Health Technol Assess 2006; 10(32):iii-xii, 1.
61. Thompson-Coon J., Castelnuovo E, Pitt M, Cramp M, Siebert U, Stein K. Case finding for hepatitis C in primary care: a cost utility analysis. Fam Pract 2006; 23(4):393-406.
62. Foster GR, Goldin RD, Main J, Murray-Lyon I, Hargreaves S, Thomas HC. Management of chronic hepatitis C: clinical audit of biopsy based management algorithm. BMJ 1997; 315(7106):453-458.
63. de Jong DJ, de Vries MJ, Boonman-de Winter LJ, van WP. Referral of hepatitis C virus seropositive patients in primary care in the Netherlands. Neth J Med 2008; 66(1):42-43.



Chapter 4

Future methods of identification



Chapter 4.1

Follow-up of mild ALT elevation identifies hidden hepatitis C in primary care

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Accepted for publication in the British Journal of General Practice

Abstract

Introduction: Hepatitis C (HCV) and hepatitis B (HBV) virus infection can lead to serious complications if left untreated, but often remain undetected in primary care. Mild alanine aminotransferase (ALT) elevations (30-100 IU/L) are commonly found and could be associated with viral hepatitis. Unfortunately these findings frequently remain without follow-up.

Aim: To determine if and how mild ALT elevation can be used to identify hidden HCV and HBV infection in primary care.
Design: Cross-sectional cohort study
Setting: Primary care patients referred for liver enzyme testing were selected by a large primary care diagnostic centre (Saltro).

Methods: First, 750 anonymous samples were collected in three categories of ALT elevation (30-50IU/L, 50-70IU/L, 70-100IU/L) and tested for HCV and HBV. Second, the national prevalence of each ALT elevation was estimated by analyzing all annual ALT tests performed at Saltro.

Results: HCV prevalence was 1.6% and 1.2% in patients with an ALT of 50-70 and 70-100IU/L respectively. In patients with an ALT of 30-50IU/L HCV-prevalence was normal (≤0.1%). HBV prevalence was normal (≤0.4%) in all groups. The estimated national number of ALT tests performed annually in primary care was 1.1 million. An ALT of 30-50IU/L was found in 21.1%, an ALT of 50-70IU/L in 5.6% and 2.6% had an ALT of 70-100IU/L.

Conclusion: In primary care patients with an ALT level of 50-100IU/L, HCV prevalence is tenfold the population prevalence whereas HBV prevalence is not elevated. Therefore follow-up HCV-testing is indicated in these patients, even when other explanations for ALT elevation are present.

Introduction

Infection with viral hepatitis, especially hepatitis C virus (HCV) is increasingly considered as a serious health threat in today's society. Unfortunately, this disease still remains relatively unknown among the general population and general practitioners (GPs) in countries with a low infection rate. It is estimated that 2-3% of the world population (123-170 million people) is infected with HCV and 5-6% (350 million) with chronic hepatitis B (HBV), of which a large proportion remains undiagnosed.[1-3] If no treatment is started, approximately 20% of the chronic HCV and HBV carriers will develop liver cirrhosis of whom roughly 5% will develop hepatocellular carcinoma.[4,5]

Fortunately, treatment outcomes of viral hepatitis have improved considerably in the past decade, especially for HCV. Success rates for HCV and HBV treatment are dependant on genotype. At present 50 to 80% of chronic HCV carriers can be cured. Chronic HBV can be suppressed in 35% (HBeAg loss) and cured in 7% of cases (HBsAg loss).[6]

Despite the serious consequences of infection, only a small proportion of HCV and HBV carriers are presently diagnosed. The main reasons are the lack of specific clinical symptoms and the limited awareness of viral hepatitis among physicians. The problem of underdiagnosing is most pressing for HCV carriers. At present, only a fraction of the estimated 15,000 to 60,000 chronic carriers in The Netherlands are diagnosed.[7] Since the virus is transmitted through blood-to-blood contact, current case finding strategies are based on the identification of risk groups. The most important risk groups for HCV are presented in Box 1.[8-10]

Box 1. Risk groups for hepatitis C[8-10]

- past and present hard drug users, in particular injecting drug users
- immigrants from highly endemic countries (prevalence >10%)
- recipients of blood (-products) before 1992
- travellers whose skin was pierced in endemic countries (prevalence >2%)
- professionals at occupational risk
- HIV-infected men who have sex with men

Even though identification and testing of these risk groups can improve case finding, this will lead to the detection of only a small sample of infected individuals. A recent survey showed that a national HCV campaign in the Netherlands is expected to detect an additional 500 HCV patients, still leaving the majority of the HCV infected population undiagnosed.[11] Therefore, additional case finding strategies in clinical practice are required.

The ALT test is the most frequently used test for liver disease in primary care. An ALT test result of >100 IU/L is a clear indicator of serious liver disease, but a mildly elevated ALT result (30 to 100) is often ascribed to the use of medication (for example statins) or alcohol, obesity, or for lower ALT levels (<50), considered as part of the normal distribution of test results. As a consequence, abnormal ALT levels are frequently accepted without adequate diagnostic follow up.[12]

Several international studies have reported a substantially increased risk of viral hepatitis in patients with mildly elevated alanine aminotransferase (ALT) levels.[13-17] To determine if and how mild ALT elevation found in daily primary care practice can be used to detect hidden HCV and HBV infection, the prevalence of viral hepatitis and a cut-off point above which a substantially increased risk of viral hepatitis is present, need to be determined.

Aims

The aim of our study is to determine if primary care patients with mild ALT elevation are at increased risk for HCV and HBV infection, and if so, to establish a cut-off point above which routine follow-up for viral hepatitis is effective in daily practice.

Methods

A cross-sectional cohort study was performed among primary care patients referred for liver enzyme testing to the Saltro Diagnostic Centre, the leading primary care laboratory in the centre of the Netherlands. The Saltro Diagnostic Centre operates from 135 locations in the Netherlands, processes diagnostic applications for 600,000 patients annually and offers laboratory facilities to approximately 750 primary care physicians in 350 surgeries.

As a first step, patients referred by their general practitioner for liver enzyme testing with a mildly elevated ALT test result (30 to 100 IU/L) were identified anonymously. Patients for whom an additional HCV or HBV test was ordered were not included. Samples were collected in three groups with different ranges of mild ALT elevation (30-50 IU/L, 50-70 IU/L, 70-100 IU/L). For each group, every third patient was selected for additional testing to prevent contamination bias, until each group contained 250

samples. Data collection for these 750 samples took place from January to June 2010. In these samples HBV and HCV prevalence was assessed.
As the second step, to estimate the potential effect on hepatitis case finding on a national level, the prevalence of the different levels of mild ALT elevation in primary care patients who are referred for ALT testing was evaluated. For his purpose, all the ALT test results of patients referred for an ALT test by a general practitioner to the Saltro Diagnostic Centre from July 2009 to June 2010 were analysed. These data were extrapolated based on the number of GPs in the Saltro database and the national number of GPs on January first 2010, as demonstrated by a national survey of GP registrations performed by the Netherlands Institute of Health Services Research (Nivel).[18] To validate the extrapolation, it was repeated based on the number of primary care surgeries in both the Saltro database and in the Netherlands as found in the Nivel survey.[18]

Laboratory tests
All patients were tested for HCV using ELISA testing for anti-HCV. Positive tests were confirmed by immunoblot analysis. PCR was performed to determine if chronic infection had taken place. Chronic HBV was determined by ELISA testing for HBsAg and anti-HBc. Chronic HBV was diagnosed if both tests had a positive result.

Data collection and analysis
Anonymous data were collected through standardized procedures by staff employees of the Saltro Diagnostic Centre. Data were stored and analyzed using Excel statistical package. Where necessary due to low numbers, 95% confidence intervals were determined based on the modified Wald method developed by Agresti and Coull.[19]

Ethical considerations
After consulting the Medical-Ethics committee of the University Medical Centre Utrecht, it was decided to perform data collection and processing anonymously and to inform GPs affiliated to the Saltro diagnostic centre of the overall results of this study. It was left up to the GP whether or not to recall patients with a relevant ALT elevation to perform additional testing.

Table 1. Characteristics of the 750 bloodsamples used for hepatitis prevalence

	ALT 30-50 IU/L N=250	ALT 50-70 IU/L N=250	ALT 70-100 IU/L N=250	Total ALT 30-100 IU/L N=750
Gender – female (N)	38.4% (96)	26.4% (66)	29.6% (74)	31.5% (236)
Age – mean, years (SD)	55.5 (14.7)	53.2 (15.3)	53.4 (14.5)	54.1 (14.5)
ALT- mean, IU/L (SD)	37.6 (5.5)	58.1 (5.5)	81.8 (8.0)	59.2 (19.2)
ALT – median, IU/L (range)	36.1 (30.1-49.8)	57.4 (50.1-69.9)	81.1 (70.1-99.5)	57.4 (30.1-99.5)

Results

An overview of patient characteristics for the 750 samples used to determine the prevalence of hepatitis in the three levels of ALT elevation is shown in table 1. Table 2 demonstrates the main findings for each range of ALT test results including 95% confidence intervals. Table 3 provides an overview of the annual ALT tests performed at Saltro, including prevalence and characteristics of each level of elevation.

The overall prevalence of confirmed anti-HCV positive patients (once infected with HCV) and HCV-RNA positive patients (chronic HCV infection) was 1.1% (95%CI: 0.5-2.1%) and 0.9% (95%CI: 0.4-2.0%) respectively. The prevalence of HCV was not elevated in patients with an ALT level of 30-50IU/L. The prevalence of positive anti-HCV test results was 2.0% in the group with an ALT level of 50 to 70 IU/L and 1.2% in the group with an ALT level of 70 to 100 IU/L. The prevalence of positive HCV-RNA test results was 1.6% in the group with an ALT level of 50 to 70 IU/L and 1.2% in the group with an ALT level of 70 to 100 IU/L. Consequently the prevalence of chronic HCV was 1.4% (95%CI: 0.6-2.9%) in patients with an ALT level of 50 to 100 IU/L.

Table 2. Prevalence of hepatitis at different levels of ALT elevation compared to population prevalence

	ALT 30-50IU/L N=250	ALT 50-70IU/L N=250	ALT 70-100IU/L N=250	Population prevalence
Hepatitis C - once infected (percentage, 95%CI)	0 0.0% (0.0-1.8%)	5 2.0% (0.7-4.7%)	3 1.2% (0.2-3.6%)	0.2%[23]
Hepatitis C - chronic infection (percentage, 95%CI)	0 0.0% (0.0-1.8%)	4 1.6% (0.5-4.2%)	3 1.2% (0.2-3.6%)	0.1%[23]
Hepatitis B - chronic infection (percentage, 95%CI)	0 0.0% (0.0-1.8%)	0 0.0% (0.0-1.8%)	1 0.4% (0.0-2.5%)	0.4%[24]

Chronic HBV was found in one patient, who had an ALT level of 75 IU/L. This single finding indicates that there was no elevated HBV prevalence in all levels of mild ALT elevation.

Based on 93,637 ALT tests performed at Saltro Diagnostic Centre from July 2009 to June 2010, the number of ALT tests performed in primary care patients in the Netherlands was estimated at approximately 1.1 million annually. The tests performed at Saltro were applied for by 736 general practitioners in 356 surgeries. The national annual number of tests was calculated using the national number of practising GPs in 2010 (N=8,921) and confirmed by an extrapolation based on the number of GP-surgeries (N=4,088). Of all ALT tests performed in general practice, 68.7% had a normal ALT level (0 to 30 IU/L), 21.1% had an ALT level of 30 to 50 IU/L, 5.6% had an ALT level of 50 to 70 IU/L, 2.6% had an ALT level of 70 to 100 IU/L and 2% had an ALT level of 100 IU/L or higher. In men, the prevalence of ALT elevation was approximately twice as high as in women in all groups of ALT elevation.

When combining the national number of ALT tests with the estimated prevalence of ALT elevation of 50 to 100 IU/L in the Netherlands (8.2%), and the corresponding HCV-prevalence in this group (1.4%), an estimated 1,200 to 1,300 hepatitis C patients could be identified annually if these patients were screened for HCV.

Table 3. Characteristics of the annual ALT tests performed at Saltro

	ALT Total	ALT 0-30IU/L	ALT 30-50IU/L	ALT 50-70IU/L	ALT 70-100IU/L	ALT ≥100IU/L
Annual ALT tests and results	93,637	64,326	19,783	5,246	2,410	1,872
Percentage of total ALT tests (95%CI)	100%	68,7% (68.4-69.0%)	21.1% (20.9-21.4%)	5.6% (5.5-5.8%)	2.6% (2.5-2.7%)	2.0% (1.9-2.1%)
Mean age, years (SD)	56 (20)	56 (21)	56 (16)	53 (15)	52 (15)	51 (19)
Gender – female (N)	56.4% (52,836)	65.3% (42,037)	38.5% (7,623)	32.4% (1,700)	31.1% (749)	38.8% (727)
Mean ALT, IU/L (SD)	31 (64)	19 (5)	37 (6)	58 (6)	81 (8)	233 (393)

Discussion

Summary of main findings

The prevalence of HCV in patients with an ALT elevation of 50 to 100 IU/L was over tenfold the population prevalence, whereas the prevalence of HBV was normal.[23,24]

Only in the Netherlands, an estimated 1.1 million ALT tests were performed last year, of which 8.2% are expected to have ALT levels of 50 to 100 IU/L. If ALT is used as a tool for the identification of hepatitis C patients, this could lead to the detection of an estimated 1,200 to 1,300 cases in the first year alone. This is more than twice the number expected in a large national hepatitis C campaign aimed at the general public and hard drug users.[11]

The prevalence of ALT elevation was relatively high in men as compared to women. This is consistent with previous findings, and can be attributed to a higher prevalence of conditions that lead to an elevated ALT in men, such as cholesterol-mediated liver injury, metabolic syndrome, alcohol use, and the effect of higher hemoglobin levels.[20-22]

The GPs in the Saltro database work in a relatively urbanized area. We do not expect this to have a large effect on the number of ALT tests performed, but the HCV prevalence might be slightly higher than the mean prevalence in the Netherlands. This could lead to an overestimation of the effect on a national level.

The ALT prevalence found at an ALT level of 50 to 70 IU/L was 1.6% versus 1.2% at the higher level of 70 to 100IU/L, with largely overlapping confidence intervals. There is no rational explanation for this and we think it is due to chance.

The fact that HCV is more prevalent among patients with elevated ALT levels does not mean that ALT is an appropriate test to detect HCV. Since ALT is normal in many HCV infected patients, ALT is not fit for HCV screening. Therefore, patients at risk for HCV should be tested with an anti-HCV test (ELISA), not with ALT.

Strengths and limitations of the study

Due to ethical restrictions, data collection was performed anonymously and therefore patient characteristics were not available. Knowledge of these characteristics, such as the presence of an increased risk based on risk groups, alcohol use and medication use, BMI and previous liver disease, is generally available to general practitioners.

This additional information, which needs to be used critically because it might also mislead GPs, provides a background which increases the diagnostic value of mild ALT elevation for the identification of hidden HCV. Since information regarding risk groups is particularly helpful to identify hidden HCV, it deserves strong recommendation to at least ask for the presence of an increased risk based on the known risk groups when an elevated ALT level is found, even when other explanations for the ALT elevation are present.

Since we did not have access to patient histories, we can not confirm that the HCV patients identified in our study have not been diagnosed with HCV before. This might lead to an overestimation of the effect on case finding.

Comparison with existing literature

Our findings in the primary care population of the Netherlands are supported by findings in several international studies. Already in 2001, Sherwood and colleagues concluded that 'Abnormal results for liver function are often not adequately investigated, missing an important chance of identifying treatable chronic liver disease'.[12] Prati and colleagues demonstrated that the normal ranges for ALT are influenced by the presence of undiagnosed HCV.[22] Other international studies, performed in different populations, found an elevated prevalence of HCV in patients with elevated liver enzymes.[13-17] In these studies 5 to 10% of the total tests for liver enzymes had abnormal results.[13,15,16] The results of these studies concerning the prevalence of HCV and ALT elevation are congruent with ours. Our study specifies levels of ALT elevation at which HCV testing is indicated and therefore facilitates the use of ALT as a tool to identify hidden hepatitis C in a primary care setting.

Implications for clinical practice

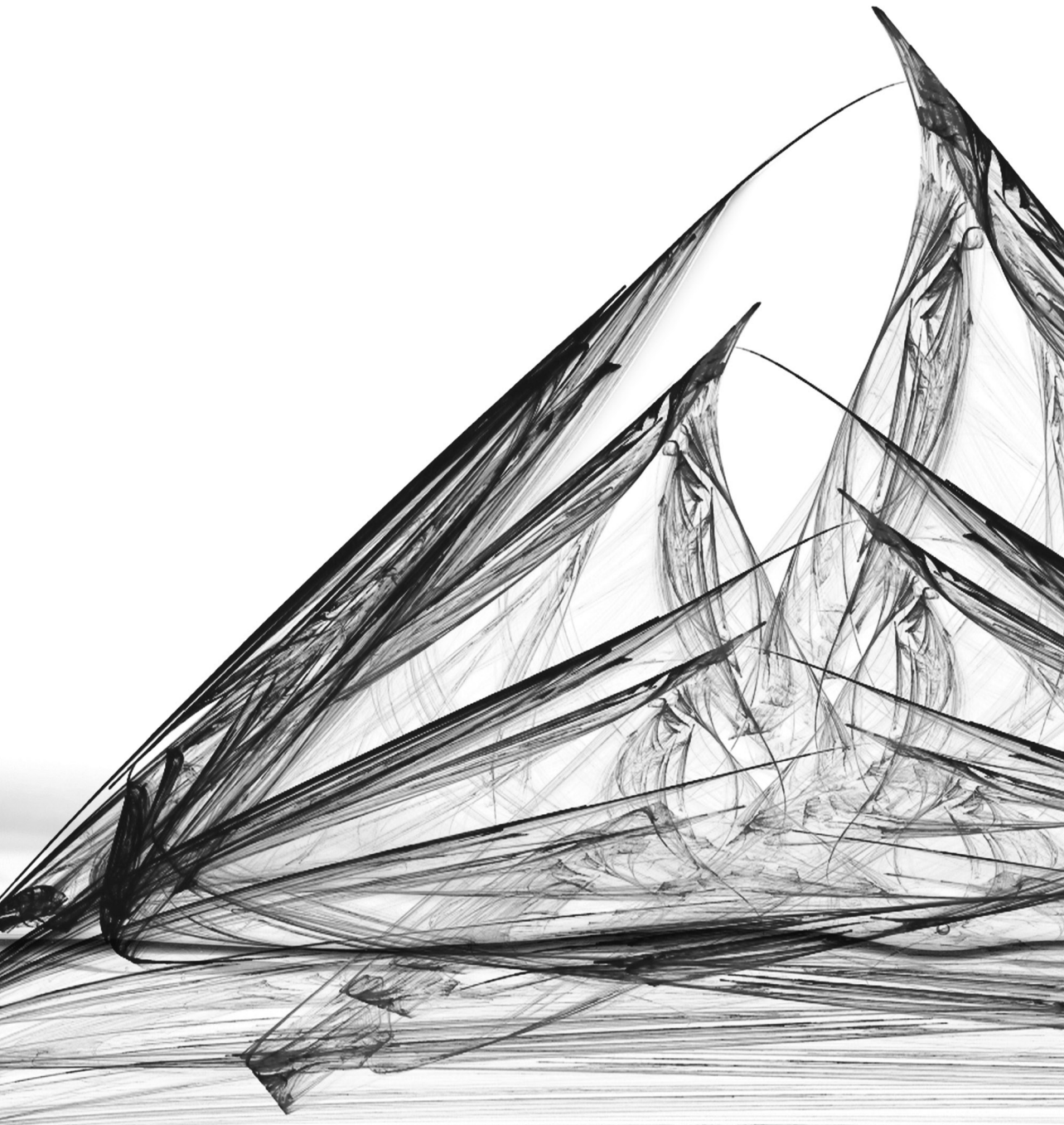
In primary care patients with an ALT elevation between 50 and 100 IU/L, the risk of HCV infection is substantially elevated whereas the risk of HBV infection is not. Therefore, we recommend that in all these patients, particularly in those for whom no clear explanation for the ALT elevation is at hand, follow-up testing for HCV is performed. In addition, we recommend enhancement of the guidelines for general practice based on these findings.

Acknowledgements
We would like to thank Mrs. van Delft and Mrs. Scheepbouwer of the Saltro Diagnostic Centre for their contribution in data collection.
Competing interests: There are no competing interests to be reported.

Reference List

1. World Health Organisation - Department of Communicable Diseases Surveillance and Response. Hepatitis B; 2002: Report no. WHO/CDS/CSR/LYO/2002.2
2. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis. 2005; 5(9):558-567.
3. World Health Organisation. Hepatitis C: global prevalence. Wkly Epidemiol Rec. 1997; 72(46):341-344.
4. Ikeda K, Saitoh S, Suzuki Y, et al. Disease progression and hepatocellular carcinogenesis in patients with chronic viral hepatitis: a prospective observation of 2215 patients. J Hepatol. 1998; 28(6):930-938.
5. Lauer GM, Walker BD. Hepatitis C virus infection. N Engl J Med. 2001; 345(1):41-52.
6. Janssen HL, van Zonneveld M, Senturk H, et al. Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomised trial. Lancet. 2005; 365(9454):123-129.
7. Health Council of the Netherlands: Committee on hepatitis C. Detection and treatment of people with hepatitis C. Rijswijk: Health Council of the Netherlands, 1997; publication no. 1997/19. ISBN 90-5549-180-2
8. Clarke A, Kulasegaram R. Hepatitis C transmission - where are we now? Int J STD AIDS. 2006; 17(2):74-80.
9. Kok A, Zuure FR, Weegink CJ, et al. Hepatitis C in the Netherlands: sparse data on the current prevalence and the necessity for epidemiological studies and innovative methods for detecting infected individuals. Ned Tijdschr Geneeskd. 2007; 151(43):2367-2371.
10. The National Institute for Public Health and the Environment (RIVM). Guideline Hepatitis C. 2011.
11. Helsper CW, Borkent-Raven BA, De Wit NJ, et al. Cost-effectiveness of targeted screening for hepatitis C in The Netherlands. Epidemiol Infect. 2011;1-12. DOI:10.1017/S0950268811000112
12. Sherwood P, Lyburn I, Brown S, et al. How are abnormal results for liver function tests dealt with in primary care? Audit of yield and impact. BMJ. 2001; 322(7281):276-278.
13. Clark JM, Brancati FL, Diehl AM. The prevalence and etiology of elevated aminotransferase levels in the United States. Am J Gastroenterol. 2003; 98(5):960-967.
14. Mathiesen UL, Franzen LE, Fryden A, et al. The clinical significance of slightly to moderately increased liver transaminase values in asymptomatic patients. Scand J Gastroenterol. 1999; 34(1):85-91.
15. McLernon DJ, Donnan PT, Ryder S, et al. Health outcomes following liver function testing in primary care: a retrospective cohort study. Fam Pract. 2009; 26(4):251-259.
16. Pendino GM, Mariano A, Surace P, et al. Prevalence and etiology of altered liver tests: a population-based survey in a Mediterranean town. Hepatology. 2005; 41(5):1151-1159.
17. Chiang JC, Lin CY, Wang JH, et al. Identifying hepatitis C virus: endemic areas and estimating the viral antibody prevalence based on the prevalence of ALT elevation. Trans R Soc Trop Med Hyg. 2009; 103(9):917-923.
18. Netherlands Institute of Health Services Research (NIVEL). GP registration numbers - 2010 survey. [in Dutch; Cijfers uit de registratie van huisartsen - peiling 2010]. 2011.
19. Agresti A, Coull BA. Approximate is better than "exact" for interval estimation of binomial proportions. Am Stat. 1998; 52(2):119-126.
20. Chen SC, Yeh JJ, Chang MH, et al. Gender difference of alanine aminotransferase elevation may be associated with higher hemoglobin levels among male adolescents. PLoS One. 2010; 5(10):e13269.
21. Bos MB, de Vries JH, Wolffenbuttel BH, et al. The prevalence of the metabolic syndrome in the Netherlands: increased risk of cardiovascular diseases and diabetes mellitus type 2 in one quarter of persons under 60. Ned Tijdschr Geneeskd. 2007; 151(43):2382-2388.

22. Prati D, Taioli E, Zanella A, et al. Updated definitions of healthy ranges for serum alanine aminotransferase levels. Ann Intern Med. 2002; 137(1):1-10.
23. Slavenburg S, Verduyn-Lunel FM, Hermsen JT, et al. Prevalence of hepatitis C in the general population in the Netherlands. Neth J Med. 2008; 66(1):13-17.
24. Marschall T, Kretzschmar M, Mangen MJ, et al. High impact of migration on the prevalence of chronic hepatitis B in the Netherlands. Eur J Gastroenterol Hepatol. 2008; 20(12):1214-1225.



Chapter 5

General discussion

General discussion

Aim of this thesis

The aim of this thesis is to improve case finding of hepatitis C by evaluating the effectiveness and the economic consequences of a variety of new case finding strategies developed for public health and primary care practice.

Summary of results

Chapter 1 provides an overview of why improvements in case finding of hepatitis C are important. *Chapter 2* demonstrates that increased efforts in case finding strategies to reach the target population and medical professionals are worth the effort. *Chapter 2.1* shows that a public campaign aimed at increasing awareness and case finding of HCV in the general population can be effective, but only with a supplementary support programme for primary care. In *Chapter 2.2* we conclude that in a campaign aimed at HCV case finding among injecting and non-injecting hard drug users, pro-actively offering HCV consultation and testing by professionals in addiction care organisations is essential to attain effect. *Chapter 3* illuminates the economic side of HCV case finding. *Chapter 3.1* demonstrates that if a case finding strategy is found to be clearly effective it is also likely to be cost-effective. For high-risk populations such as hard drug users the gain in effect is relatively high and costs of case finding can be kept low. In *Chapter 3.2* the current costs of HCV treatment in daily practice in the Netherlands, in relation to treatment outcome and side effects, are discussed. Although success rates have improved substantially in the past decades, the current costs of unsuccessful treatment and side effects are high. *Chapter 3.3* shows the effectiveness and cost-effectiveness of a nationwide hepatitis C campaign and its interventions in the Netherlands. The intervention aimed at hard drug users in addiction care was clearly effective and cost-effective. The intervention aimed at risk groups in the general population showed only a moderate effect, leading to considerable uncertainty about cost-effectiveness. This could in part be contributed to the unfavourable circumstances of its implementation. However, the overall number of HCV carriers identified by this large scale campaign remains moderate as it would only identify approximately 1% of the hidden hepatitis C carriers in the Netherlands. *Chapter 4* describes the effect of a new HCV case finding strategy in primary care practice. We demonstrate that routine testing for HCV in patients with an ALT elevation of 50 to 100IU/L could theoretically lead to the identification of an estimated 1,200 to 1,300 chronic HCV carriers. This strategy can be implemented in clinical practice guidelines in the near future.

Lessons learned

Based on the findings in this thesis the following main conclusions can be drawn:

- Involving general practitioners (GPs) and addiction care workers is fundamental for success in HCV case finding interventions.
- Increased alertness of HCV among general practitioners in clinical practice can substantially contribute to HCV case finding.
- HCV case finding strategies are more likely to be effective and cost-effective when they are focussed on risk groups with a relatively high risk.
- Mass media campaigns alone are insufficient to fully counter the problem of inadequate HCV case finding in today's society.

The role of general practice

In a case finding strategy targeting risk groups in the general population, informing and involving GPs was equally important to informing the population itself. This academic detailing of GPs should be facilitated, for instance by the use of practice facilitators, to effectively involve them in HCV case finding.

The finding that the GP plays a key role in HCV case finding in the general population is not surprising. Because of the long term personal contact of GPs with their patients, the knowledge of the patients' background and consequently their HCV risk profile is unrivalled. Therefore, hepatitis C should become as familiar to the GP as its alphabetical predecessors A and B. Luckily, the required changes in clinical practice are not too complex and HCV tests are cheap and widely available.

If all GPs become aware of the following messages, HCV case finding could improve dramatically in the years to come:

- Hepatitis C infection is generally asymptomatic but has life threatening long term complications.
- Diagnosis of HCV should not be focussed on symptoms but on testing in high-risk populations.
- Treatment is intense but successful and basically all infected patients should be referred.

To improve HCV case finding in general practice, awareness and knowledge of the risk groups is necessary. GPs should know about the following risk groups for whom HCV testing is indicated:

- past or present hard drug users (injecting and non-injecting);
- all patients with HIV, especially men who have sex with men (MSM);
- all patients with skin punctures obtained in non-Western countries, excluding earrings;

- patients with an ALT of over 50IU/L, especially if unexplained;
- all patients with a blood transfusion or organ transplantation before 1992;
- first generation immigrants from developing countries in Central Africa, Asia and South America and from Egypt and South-East Europe excluding Turkey.

Guidelines, such as those of The Dutch College of General Practitioners (NHG, website: nhg.artsennet.nl) and the World Health Organisation (WHO, website: www.who.int) can provide more detailed information on HCV risk groups.

In daily primary care practice, the desirability of testing needs to be discussed with each individual patient at risk to balance its benefits and burden. In this discussion, dilemmas may arise:
Should a 85 year old lady who has had a blood-transfusion 25 years ago be tested? Should an illegal immigrant or hard drug user be tested if they do not have the necessary insurance or are not in adequate personal circumstances to be treated?
In practice, for some patients at risk successful treatment may seem very unlikely. Still, for these patients valid motives for HCV testing apply, such as protection of caretakers and family members, knowledge of prognosis, or just a patients wish to be informed. Moreover, treatment possibilities and burden vary substantially for patients with different personal and disease characteristics. As a result, adequate assessment of the suitability for treatment for each individual patient is too complex for GP's. Therefore, HCV testing should be performed unreservedly in case of an increased risk and basically all patients tested positive for HCV should be referred to an expert HCV treatment centre. Since treatment possibilities and knowledge of HCV are evolving fast, only these expert centres can adequately assess and discuss the treatment possibilities and provide up-to-date information on HCV for the individual patient.

The role of addiction care

In the Netherlands, the popularity of injecting drug use is gradually decreasing and recent interventions by public health services have reduced HCV transmission rates in this population.[1-3] However, HCV infection remains a very serious problem among injecting drug users.[3,4] Even though injecting drug users are often considered as a complex group for treatment, recent research demonstrates that adherence to treatment in this group is sufficient and treatment success rates are comparable to those in non-injecting drug users.[5-7] Moreover, even though re-infection does occur, re-infection rates among hard drug users after being cured can be kept low if adequate guidance after treatment is provided.[8-10] Consequently, addiction care remains a very important setting for HCV case finding. This thesis demonstrates that a pro-active HCV case finding policy is effective and cost-effective in addiction care. Unfortunately, HCV case finding is currently not prioritized in all addiction care organisations. Therefore, the main lesson to be learned

for addiction care is that case finding among hard drug users and particularly in current and previously injecting drug users deserves full attention.

The role of the public health services

Some important groups at risk for HCV are not sufficiently reached by GPs or addiction care workers. Particularly men who have sex with men (MSM) infected with the human immunodeficiency virus (HIV) are an emerging HCV risk group, with increased risk of serious complications due to the combined HCV/HIV infection. In the urbanized areas of the Netherlands the public health services (GGD) are in the best position to address this risk group. Furthermore, it was through monitoring by the public health services of Amsterdam that HIV positive MSM were identified as an emerging and important risk group in the Netherlands.[11-13] The same goes for case finding among isolated, less integrated immigrant populations and people at the edge of society such as the homeless and travellers. These risk groups require a tailored approach. Public health services in urbanized areas have better access to, and are more familiar with addressing these hard-to-reach populations at risk of HCV and therefore have an important role in improving case finding.

The role of policy makers

Of the estimated 15,000 to 60,000 HCV carriers in the Netherlands only a minority has been diagnosed.[14,15] So far, the number of patients found in even the most effective strategies is not impressive. In an extensive national HCV campaign such as ours, approximately 300 chronically infected hepatitis C patients have been identified. Mass media campaigns targeting the general public, and especially those that do not actively involve health care professionals, seem to add little to HCV case finding. This supports the current government policy not to endorse large scale mass media campaigns.

In the theoretical situation that the strategy based on HCV testing in all primary care patients with the designated elevated ALT levels would be optimally implemented, the number of HCV carriers diagnosed nationwide could be increased to approximately 1,500. Again this is only a minority of undiagnosed HCV carriers, indicating that the challenge of adequate case finding and the need for finding and funding new successful approaches in HCV case finding remains.

We have demonstrated that targeted case finding in high-risk groups involving health care professionals is likely to be cost-effective. Now it is up to policy makers and health insurance companies to facilitate the implementation of these strategies.

Recommendations for future HCV case finding

The quest for improving case finding strategies for hepatitis C is far from over. This thesis has provided new insights on which strategies are effective and, maybe even more important, which strategies are not. To further improve HCV case finding, several approaches need to be explored.

Electronic patient databases, based on practice registration data, are the standard in primary care. In many countries these 'health information systems' (HIS) generate automated warnings, for instance in case of possible interactions between prescribed medications. Similarly, these systems could support HCV case finding by alerting the GP when a patient in daily practice is at risk of HCV. In addition, the system could be used for screening the entire patient population for those with HCV risk factors. Such electronic support is currently not feasible because the country of origin, risk behaviour and previous transfusions are not reported in a standardized way in the HIS. Since electronic support could greatly improve patient identification in clinical practice, we advise ICT decision support to be included in future case finding strategies. For patients with an ALT of 50 to 100IU/L or a HBV or HIV infection an automated recommendation for follow-up testing could be issued by the laboratory doing the test. In addition, to prevent misinterpretation of the anti-HCV test result, laboratories who report a positive anti-HCV test should either provide a warning that an RNA-test is indicated or automatically perform one.

Internet-based risk-assessment for HCV, including a letter of referral for testing in case of increased risk, may prove a useful approach in improving HCV detection in the population.[16,17] This low-cost intervention may help to overcome barriers due to its anonymous and easy access and is previously demonstrated to be effective for hard-to-reach-populations.[17] Therefore, the use of similar Internet or other web-based interventions deserves further implementation and evaluation in the future.

To improve case finding in the immigrant population at increased risk of HCV, 'screening at the gate' (i.e. medical examination on entry of the country) could help to overcome barriers for finding high-risk immigrants. Currently immigrants are already checked for tuberculosis. Extending this screening with HCV testing for immigrants at risk would be relatively easy, legitimate and is likely to be cost-effective.

Finally, we suggest a more integrated approach in screening for various infectious diseases. Given the overlap in modes of transmission and risk groups, combined screening for HCV, hepatitis B (HBV) and Human immunodeficiency virus (HIV) needs to be considered. An integrated approach is likely to benefit compliance of both health care professionals and target populations. GPs and addiction care workers are busy professionals, who need to prioritize to stay up to date with all relevant developments in

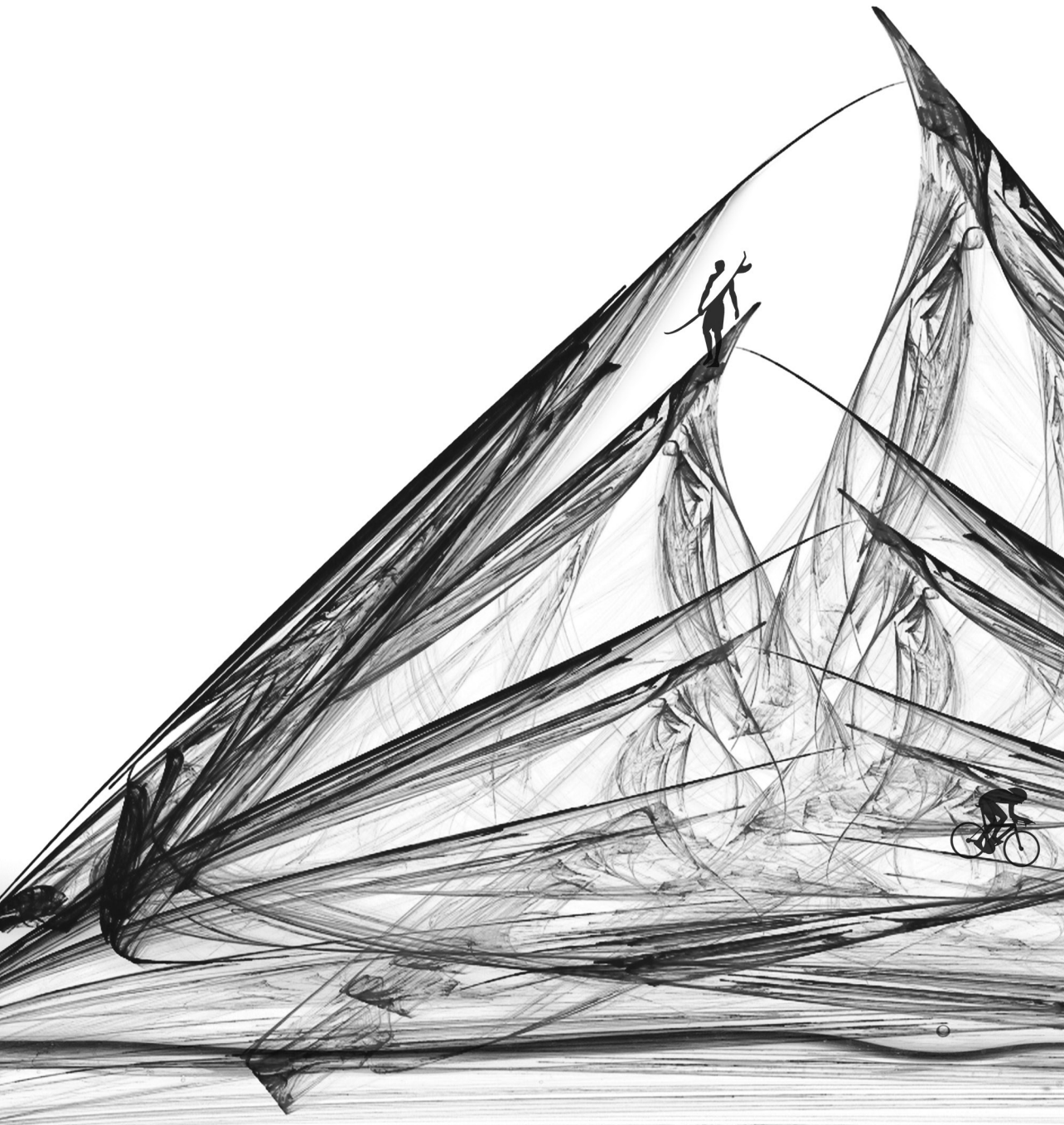
their extensive domains. This makes a combined approach more appealing. Populations at risk are likely to be more interested in a campaign providing combined information concerning several diseases, instead of repeated and separate approaches for each individual disease. Therefore, a combined campaign for HCV, HBV and HIV should be considered for future case finding strategies.

In today's society, mass media play a major role as a source of information. To compete with other news, information is often oversimplified and lacking nuance. This lack of nuance can lead to inducing fear instead of awareness. For hepatitis C, 99.6% of the Dutch population is not infected and the majority of the population is not at the slightest risk. Therefore some restraint in increasing awareness seems indicated. Based on the cost-effectiveness analyses, Benjamin Franklin seems right saying that 'an ounce of prevention is worth a pound of cure' (in Dutch: 'Beter voorkomen dan genezen').[18] But on the other hand, the Dutch called poet 'Nicolaas Beets' once eloquently illuminated the downside of awareness. He stated 'one suffers most from the suffering one fears, but has never come to be' (in Dutch: 'Een mens lijdt dikwijls het meest door het lijden dat hij vreest, doch dat nooit op zal dagen').[19] Therefore, even though early identification of hepatitis C seems to meet the criteria of Wilson and Junger, future hepatitis C awareness and identification campaigns should be strictly evaluated and targeted only at those who are at a substantially increased risk.[20]

Reference List

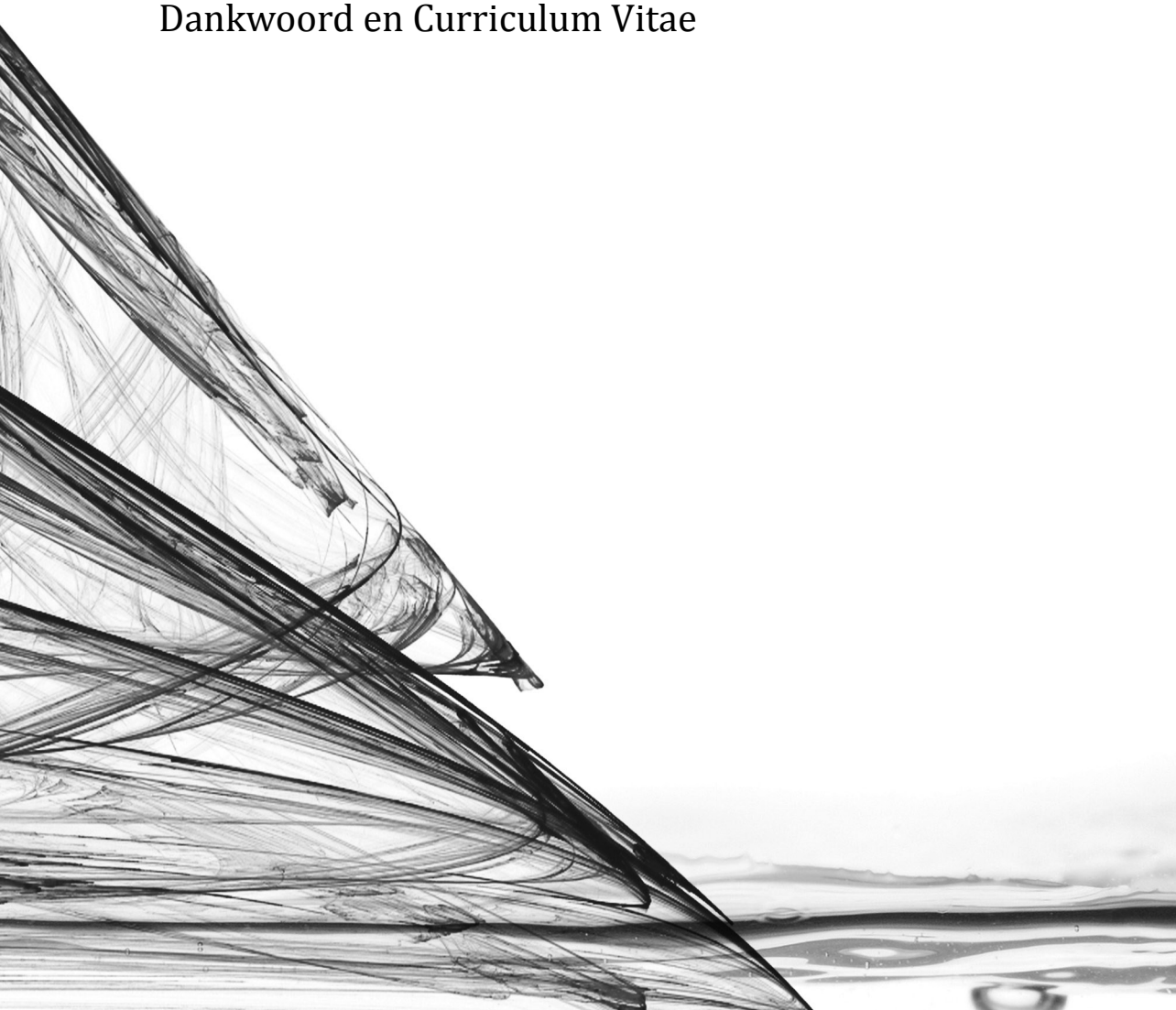
1. van den BC, Smit C, Van BG, Coutinho R, Prins M. Full participation in harm reduction programmes is associated with decreased risk for human immunodeficiency virus and hepatitis C virus: evidence from the Amsterdam Cohort Studies among drug users. Addiction 2007; 102(9):1454-1462.
2. van den Berg CH, Smit C, Bakker M, Geskus RB, Berkhout B, Jurriaans S et al. Major decline of hepatitis C virus incidence rate over two decades in a cohort of drug users. Eur J Epidemiol 2007; 22(3):183-193.
3. van de Laar TJ, Langendam MW, Bruisten SM, Welp EA, Verhaest I, van Ameijden EJ et al. Changes in risk behavior and dynamics of hepatitis C virus infections among young drug users in Amsterdam, the Netherlands. J Med Virol 2005; 77(4):509-518.
4. Nelson PK, Mathers BM, Cowie B, Hagan H, Des JD, Horyniak D et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. Lancet 2011.
5. Grebely J, Matthews GV, Hellard M, Shaw D, van B, I, Petoumenos K et al. Adherence to treatment for recently acquired hepatitis C virus (HCV) infection among injecting drug users. J Hepatol 2011; 55(1):76-85.
6. Hellard M, Sacks-Davis R, Gold J. Hepatitis C treatment for injection drug users: a review of the available evidence. Clin Infect Dis 2009; 49(4):561-573.
7. Lindenburg CE, Lambers FA, Urbanus AT, Schinkel J, Jansen PL, Krol A et al. Hepatitis C testing and treatment among active drug users in Amsterdam: results from the DUTCH-C project. Eur J Gastroenterol Hepatol 2010.
8. Grebely J, Knight E, Ngai T, Genoway KA, Raffa JD, Storms M et al. Reinfection with hepatitis C virus following sustained virological response in injection drug users. J Gastroenterol Hepatol 2010; 25(7):1281-1284.
9. van de Laar TJ, Molenkamp R, van den BC, Schinkel J, Beld MG, Prins M et al. Frequent HCV reinfection and superinfection in a cohort of injecting drug users in Amsterdam. J Hepatol 2009; 51(4):667-674.
10. Backmund M, Meyer K, Edlin BR. Infrequent reinfection after successful treatment for hepatitis C virus infection in injection drug users. Clin Infect Dis 2004; 39(10):1540-1543.
11. van de Laar TJ, van der Bij AK, Prins M, Bruisten SM, Brinkman K, Ruys TA et al. Increase in HCV incidence among men who have sex with men in Amsterdam most likely caused by sexual transmission. J Infect Dis 2007; 196(2):230-238.
12. van de Laar TJ, Pybus O, Bruisten S, Brown D, Nelson M, Bhagani S et al. Evidence of a large, international network of HCV transmission in HIV-positive men who have sex with men. Gastroenterology 2009; 136(5):1609-1617.
13. Urbanus AT, van de Laar TJ, Stolte IG, Schinkel J, Heijman T, Coutinho RA et al. Hepatitis C virus infections among HIV-infected men who have sex with men: an expanding epidemic. AIDS 2009; 23(12):F1-F7.
14. Health Council of the Netherlands: Committee on hepatitis C. Detection and treatment of people with hepatitis C. 1997/19. 1997. Rijswijk.
15. Kretzschmar MEE. The prevalence of hepatitis C in the Netherlands - Report for ministry of Welfare and Sports [in Dutch: De prevalentie van hepatitis C in Nederland]. notitie RIVM . 2-12-2004.
16. Zuure F, Davidovich U, Kok G, Depla AC, Hoebe C, van den HA et al. Evaluation of a risk assessment questionnaire to assist hepatitis C screening in the general population. Euro Surveill 2010; 15(15):19539.
17. Zuure FR, Davidovich U, Coutinho RA, Kok G, Hoebe CJ, van den HA et al. Using mass media and the Internet as tools to diagnose hepatitis C infections in the general population. Am J Prev Med 2011; 40(3):345-352.
18. Richard Saunders (pseudonym of Benjamin Franklin), Poor Richard's Almanack, 1733 - 1748.

19. Buddingh C. Citaten & aforismen. Utrecht: Het Spectrum, 2003. 1051 blz. ISBN 90 274 9051 1. page 516. Probably after M. de Montaigne (1533-1592): "Qui craint de souffrir, il souffre déjà de ce qu'il craint" - Essais, book III, 13; cited after Guerlac, "Citations françaises", p. 23. 1961.
20. Wilson JMG, Jungner G. Principles and practice of screening for disease. Public Health Papers nr 34. Geneva: WHO. 1968.



Chapter 6

Nederlandse Samenvatting
Dankwoord en Curriculum Vitae



Nederlandse samenvatting

Hepatitis C is een via bloed overdraagbare leverziekte die kan leiden tot ernstige leverschade en leverkanker. In Nederland zijn naar schatting 15.000 tot 60.000 mensen geïnfecteerd, maar omdat klinische verschijnselen tijdens een infectie vaak ontbreken zijn deze personen moeilijk op te sporen. De behandeling is de laatste jaren sterk verbeterd waardoor hepatitis C een behandelbare ziekte is geworden. Hierdoor is de noodzaak tot opsporing toegenomen.

Het doel van dit proefschrift is om de opsporing van hepatitis C te verbeteren door verschillende strategieën voor opsporing van hepatitis C te evalueren op effectiviteit en kosteneffectiviteit. Daarbij wordt aandacht besteed aan nieuwe opsporingsstrategieën, nieuwe doelgroepen, kosten van hepatitis C behandeling en de rol van verschillende zorgprofessionals.

Hoofdstuk 2 laat zien dat nieuwe, intensievere strategieën voor de opsporing van hepatitis C tot betere resultaten kunnen leiden. In *Hoofdstuk 2.1* wordt de meerwaarde van een ondersteuningsprogramma voor huisartspraktijken geëvalueerd, in een massamediale campagne gericht op het opsporen van hepatitis C in het algemeen publiek. Hieruit blijkt dat een campagne gericht op risicogroepen in de algemene bevolking effectief kan zijn bij de opsporing van hepatitis C door verhoging van het bewustzijn, maar alleen als huisartspraktijken gerichte ondersteuning krijgen. In *Hoofdstuk 2.2* worden twee opsporingstrategieën voor hepatitis C in de verslavingszorg met elkaar vergeleken. Bij beide strategieën worden in de verslavingszorginstellingen posters en folders verspreid met informatie over hepatitis C en de noodzaak tot testen. In de eerste strategie wordt er vervolgens alleen op hepatitis C getest als hier door de hard drug gebruiker zelf om gevraagd wordt. In de andere strategie worden de hard drug gebruikers actief benaderd door de verslavingszorgmedewerkers en gevraagd om deel te nemen aan voorlichtingsgesprekken en zo nodig een hepatitis C test. Dit onderzoek laat zien dat een strategie waarbij hard drug gebruikers actief benaderd worden, een positief effect op de opsporing van hepatitis C heeft terwijl de reactieve benadering geen effect laat zien. Daarom wordt geconcludeerd dat een actieve benadering van hard drug gebruikers onmisbaar is voor een betere opsporing van hepatitis C in de verslavingszorg.

Hoofdstuk 3 belicht de economische aspecten van hepatitis C opsporing. *Hoofdstuk 3.1* beschrijft een kosteneffectiviteitanalyse van de in *Hoofdstuk 2* beschreven opsporingsstrategieën. Daaruit blijkt dat alleen de meer intensieve opsporingsstrategieën, dus de strategie voor het algemeen publiek waarbij huisartsen ondersteund worden en de strategie met een actieve benadering in de verslavingszorg, kosteneffectief zijn.

In *Hoofdstuk 3.2* worden de actuele kosten van hepatitis C behandeling in Nederland in kaart gebracht. Deze kosten worden apart beschreven voor de verschillende uitkomsten van de behandeling, voor verschillende patiëntkarakteristieken en voor de componenten

van de behandeling. Deze analyse laat zien dat, ondanks dat de behandeling van hepatitis C de laatste decennia sterk is verbeterd, de actuele kosten als gevolg van niet-succesvolle behandelingen en bijwerkingen nog steeds hoog zijn. De kosten van hepatitis C behandeling worden voornamelijk bepaald door de duur van behandeling, de medicatiekosten en de kosten van bijwerkingen. *Hoofdstuk 3.3* beschrijft de kosteneffectiviteit van de 'Nationale hepatitis C campagne', zoals die in Nederland uitgevoerd is van 2009 tot en met 2011. Deze campagne was gericht op het verhogen van het bewustzijn van hepatitis C bij risicogroepen en zorgprofessionals en het actief opsporen van mensen die besmet zijn met het hepatitis C virus. De Nationale hepatitis C campagne bestond uit twee afzonderlijke interventies. Eén interventie betrof een massamediale campagne gericht op risicogroepen in het algemeen publiek, waarbij ondersteuning voor de huisartspraktijken beschikbaar was. De andere interventie was gericht op hard drug gebruikers in de verslavingszorg, waarbij aan hen actief informerende gesprekken en zo nodig een hepatitis C test aangeboden werd. Alleen de interventie die uitgevoerd werd in de verslavingszorg liet een duidelijk kosteneffectief effect zien. De interventie gericht op risicogroepen in het algemene publiek liet slechts een beperkt effect zien met teveel onzekerheid over de kosteneffectiviteit om hieraan conclusies te mogen verbinden. Het gezamenlijke effect van beide interventies was beperkt, wat leidt tot de conclusie dat het onwaarschijnlijk is dat dit soort landelijke campagnes alleen, effectief genoeg zijn om de opsporing van hepatitis C in Nederland voldoende te verbeteren. Ontwikkeling van nieuwe opsporingsstrategieën blijft dus gewenst.
Hoofdstuk 4 beschrijft een dergelijke nieuwe strategie. *Hoofdstuk 4.1* laat zien dat bij eerstelijns patiënten bij wie bij routine laboratorium onderzoek een afwijkende leverfunctietest (ALAT) gevonden wordt van 50 tot 100 IU/L, meer dan tien keer zoveel hepatitis C voorkomt dan bij patiënten met een normale ALAT uitslag (hepatitis C prevalentie 1.4%). Op grond hiervan raden wij huisartsen aan om bij patiënten met een ALAT van 50 tot 100 IU/L een anti-HCV test uit te voeren, of op zijn minst door te vragen naar de aanwezigheid van risicofactoren voor hepatitis C. Hiermee zouden naar schatting 1.200 tot 1.300 chronische hepatitis C dragers extra kunnen worden opgespoord in Nederland.
Hoofdstuk 5 beschrijft de belangrijkste conclusies uit de resultaten van de studies in dit proefschrift en de rol van verschillende zorgprofessionals bij de opsporing van hepatitis C.

Die conclusies luiden:

- Het betrekken van huisartsen en verslavingszorgprofessionals is fundamenteel voor succes bij de opsporing van hepatitis C.
- Meer aandacht voor hepatitis C in de dagelijkse huisartspraktijk en verslavingszorg zou substantieel bijdragen aan een betere opsporing van hepatitis C.

- Opsporingsstrategieën voor hepatitis C hebben een grotere kans effectief en kosteneffectief te zijn als ze primair gericht worden op groepen met een hoog risico op hepatitis C.
- Publiekscampagnes alleen zijn onvoldoende om het probleem van de achterblijvende opsporing van hepatitis C voldoende aan te pakken.

Verschillende zorgprofessionals spelen een belangrijke rol bij de opsporing van hepatitis C.

Huisartsgeneeskunde. Bij de opsporing van hepatitis C in het algemene publiek, is het informeren en betrekken van de huisartspraktijken van even groot belang als het informeren van de risicogroepen zelf. Als huisartsen zich bewust worden van de volgende boodschappen dan zou de opsporing van hepatitis C de komende jaren drastisch kunnen verbeteren:

- Hepatitis C infectie verloopt meestal langdurig symptoomloos, maar kan levensbedreigende gevolgen hebben.
- Diagnostiek van hepatitis C is daarom niet gebaseerd op het herkennen van symptomen maar op het testen van hoogrisicogroepen.
- Behandeling is belastend, maar in toenemende mate succesvol. Patiënten geïnfecteerd met hepatitis C moeten daarom in principe verwezen worden voor een adequaat vervolgtraject.

Voor het verbeteren van de opsporing van hepatitis C zouden huisartsen en praktijkverpleegkundigen zich bewust moeten zijn van de risicogroepen bij wie testen geïndiceerd is:

- patiënten met hard drug gebruik in heden of verleden. Met name injecterend drug gebruik, maar ook het snuiven en roken van hard drugs;
- HIV besmette personen, voornamelijk mannen die seks hebben met mannen;
- personen bij wie de huid doorboord is in niet-Westerse landen, behalve in geval van oorbellen;
- personen met een ALAT boven de 50 IU/L, vooral indien geen duidelijke verklaring voorhanden is;
- personen die een bloed- of orgaantransplantatie hebben ondergaan voor 1992;
- eerste generatie immigranten uit ontwikkelingslanden in Centraal Afrika, Azie, Zuid-Amerika en uit Egypte en Zuid-Oost Europa (exclusief Turkije).

Deze risicogroepen voor hepatitis C staan ook vermeld in de betreffende NHG standaard.

Verslavingszorg. Ondanks dat de populariteit van injecterend hard drug gebruik langzaam afneemt in Nederland, is het probleem van hepatitis C infectie nog lang niet verholpen. Vooral injecterende drug gebruikers (met een geschatte hepatitis C prevalentie van 60

tot 80%), maar ook hard drug gebruikers die snuiven of roken, recent of in het verleden, hebben een verhoogde kans op hepatitis C besmetting (geschatte prevalentie 2 tot 35%). In tegenstelling tot wat professionals en patiënten soms denken zijn deze met hepatitis C besmette hard drug gebruikers vaak goed te behandelen. Daarnaast blijkt behandeling, naast een curatief effect op de hepatitis C infectie, ook vaak een gunstig effect te hebben op verslavingsgedrag en levensstijl. Gezien de aanzienlijke winst die te behalen is, verdient opsporing van hepatitis C een belangrijke plaats op de agenda van zorgverleners en beleidsmakers in de verslavingszorg.

Gemeentelijke Gezondheidsdiensten. Voor enkele moeilijk bereikbare risicogroepen, zoals dak- en thuislozen en immigranten, zijn de Gemeentelijke Gezondheidsdiensten (GGD'en) in de beste positie om de hepatitis C opsporing te coördineren. Vooral in stedelijke gebieden spelen de GGD'en een belangrijke rol in het bestrijden van hepatitis C door het aanbieden van cultuur gerichte opsporingsprogramma's aan immigranten en door een gerichte benadering van dak- en thuislozen en HIV positieve mannen die seks hebben met mannen.

Beleidsmakers. Dit proefschrift laat zien dat doelgerichte opsporing van hepatitis C met meer betrokkenheid van de verschillende zorgprofessionals zowel effectief als kosten-effectief kan zijn. Het is aan de beleidsmakers om de implementatie van de succesvolle opsporingsstrategieën voor hepatitis C te faciliteren.

Aanbevelingen voor de toekomst

Omdat de opsporing van hepatitis C nog steeds verbetering behoeft, bevelen wij voor toekomstige interventies gericht op opsporing van hepatitis C aan om:

- het gebruik van Huisartsen Informatie Systemen (HIS-en) bij klinische besluitvorming en selectie van risicogroepen verder te exploreren;
- het gebruik van web-based opsporingsprogramma's verder te ontwikkelen;
- de mogelijkheden voor 'hepatitis C screening aan de poort' onder immigranten uit hoog risico gebieden te onderzoeken en zo mogelijk routinematig op te nemen in het standaard medisch onderzoek bij entree in ons land;
- opsporingsprogramma's voor hepatitis C te combineren met programma's gericht op andere infectieziekten zoals hepatitis B en HIV.

Dankwoord

In mijn leven heb ik al heel wat mooie avonturen mogen beleven. Voor ieder avontuur bleken twee voorwaarden nodig om er echt een mooi avontuur van te maken. Enerzijds een goede basis waarvan je weet dat je er op terug kan vallen en anderzijds aangenaam gezelschap om je avontuur mee te delen. Deze promotie is ook een groot avontuur geweest. Dat het een mooi avontuur was komt ook nu weer door de mensen die voor mij de basis vormen en door alle bijzondere mensen die ik in deze onstuimige tijd om me heen heb gehad. Zonder deze mensen had dit proefschrift nooit het licht gezien, dus ik ben erg blij dat ik nu eindelijk de mogelijkheid heb om hen te bedanken.

Allereerst gaat mijn welgemeende dank uit naar mijn promotoren en co-promotor.
Prof. Dr. N.J. de Wit, geachte promotor, beste Niek. Jouw snelle, zorgvuldige en opbouwende commentaar en begeleiding hebben enorm bijgedragen aan het succes en plezier van dit promotie traject. Je consciëntieuze manier van onderzoek bedrijven en de menselijkheid waarmee jij in je vak staat vormen een bron van inspiratie waar ik ook in de toekomst uit kan blijven putten. Bedankt voor het vertrouwen waarmee je me vele mogelijkheden gegeven hebt om mij verder te ontwikkelen en zichtbaar te maken in de onderzoeks- en huisartsen wereld. Ik had me geen betere promotor kunnen wensen. Bedankt voor deze mooie en vruchtbare tijd.

Dr. G.A. van Essen, geachte co-promotor, beste Ted. Jouw 'down-to-earth' en pragmatische benadering hebben mij keer op keer herinnerd waarom ik huisartsen zulke prettige collega's vind. Daarnaast was ook jouw snelle en duidelijke commentaar, en daarbij zeker ook de prettige samenwerking met Niek, van grote invloed op mijn promotie-plezier. Bedankt voor je enorme bijdrage aan dit proefschrift.

Prof. Dr. M.J.M. Bonten, geachte 'tweede' promotor, beste Marc. Door de goede directe begeleiding is het niet erg vaak nodig geweest om een beroep te doen op mijn 'back-up' promotor, maar het was erg prettig om te weten dat een top-onderzoeker als jij ook achter me stond waar nodig.

Prof. dr. A.I.M. Hoepelman, Prof. dr. M.E. Numans, Prof. dr. H.A. Smit, Prof. dr. R.A. Coutinho en Prof. dr. M.Y. Berger, geachte leden van de beoordelingscommissie. Dank voor het beoordelen van dit proefschrift.

Daarnaast gaat mijn dank uit naar de mede-auteurs van de artikelen in dit proefschrift en de Projectgroep Landelijke Hepatitis C Campagne.
Allen bedankt voor de prettige samenwerking en jullie aandeel bij de totstandkoming van dit proefschrift. Zonder jullie was dit proefschrift er niet geweest.

En natuurlijk mijn geweldige paranimfen.
Lieve An, zonder jou was dit promotietraject ontzettend veel saaier geweest (maar wellicht wel iets korter). Mede door jouw aanwezigheid had ik 's ochtends weer zin om naar het Julius Centrum te gaan. De relativerende gesprekken en gedeelde dromen over verre reizen, maken zelfs zo'n dag waarop je alleen maar naar een computerscherm hebt zitten staren tot een plezierige aangelegenheid.

Weledelzeergeleerde voorzitter, beste Jaap, wat was mijn promotie tijd ongelooflijk veel minder bruisend geweest zonder jouw aanwezigheid. Jouw passie voor het leven is een inspiratie voor mij en vele anderen. En daarnaast hebt je me ook nog eens ingewijd in de wondere wereld van de Klamme Zemen. Bedankt voor al deze mooie toevoegingen aan de afgelopen (en komende) jaren, volgend jaar samen op de Ventoux!!

En als ik het over Jaap heb, dan kan ik alleen maar doorgaan met de rest van het PhD-life-event-team. Madeleine, Geert-Jan en Margriet, door de gedeelde life-events en dagelijkse beslommeringen werd het promotietraject niet alleen een ontwikkeling in de wetenschap, maar net zo zeer een ontwikkeling in het leven. Bedankt voor deze (en de nog komende) waardevolle ervaringen.

En dan zijn er de trouwe vrienden die samen de fundamenten vormen waarop ik deze promotie heb kunnen bouwen. Lieve Alma, Maaike, An, Janesh, Younes, Qk, Tessa, Indra, surfvrienden, Klamme Zemen, (schoon-)familie en natuurlijke alle wederhelften, bedankt voor jullie vriendschap en steun!! Zonder de basis die jullie me geven had ik dit promotietraject nooit kunnen volbrengen. Bedankt dat jullie in mijn leven zijn.
Alma, voor je heerlijke nuchterheid. Je bent als een zusje voor me. Maaike, voor je vrolijkheid. Heerlijk dat je nu mijn collega bent! Anneke, voor het delen van mijn dromen. Bedankt dat je me af en toe streng toespreekt. Janesh, voor het delen van al die avonturen. Bedankt voor alles waarvan we samen genoten hebben (huisgenoot, reisgenoot, teamgenoot, surfgenoot, UMC-genoot…..). Younes, voor onze soms pittige discussies. Ik heb veel respect voor de keuzes die je hebt durven maken. Qk, Natas, Tessa, Eva en natuurlijk jullie families, voor jullie trouwe vriendschap. Ook al zien we elkaar niet vaak, ik weet dat jullie er als trouwe vrienden zijn. Indra, bedankt dat je me bevrijd hebt van de dingen die me weerhielden om te zijn wie ik nu ben. Zonder jou was ik een minder gelukkig mens geweest. Robin, Juut en Olivier, voor de spiegel die jullie me

voorhouden als ik me weer eens ergens druk over maak. Onno, voor het combineren van goede golven en goede gesprekken. En alle Klamme Zemen maar tegelijk. Bedankt voor de gezelligheid, de vriendschap en de avonturen. Ik hoop dat ik nog lang onderdeel mag zijn van die heel bijzondere wieler-maar-vooral-vrienden-club. En sorry als jullie geleden hebben van de stress over 'hepatettes' die ik afgelopen seizoen van me afgefietst heb. Ik vrees dat ik nooit meer zo'n drive zal hebben om zo hard te fietsen..

En dan blijven er nog zoveel mensen over die ik eigenlijk allemaal persoonlijk wil bedanken;
Dr. H.M. Pieters en de rest van de staf van de huisartsopleiding voor het vertrouwen dat jullie in me gesteld hebben ondanks de keuzes die ik gemaakt heb. Mede-O2'ers en Marijke en Rebecca voor jullie flexibiliteit in het onderwijs in tijden van promotiestress. Alle medewerkers van de afdeling huisartsgeneeskunde voor jullie inspirerende aanwezigheid. Mart voor je openheid. Ardine voor jouw opgewekte steun bij mijn vuurdoop in de kosten-effectiviteit. Renée voor je introductie in de wereld van de e-learnings. Coby, rots in de branding van het Julius Centrum, voor je onaflatende vrolijke alwetendheid. Harold en Rutger voor jullie interesse in mijn sportieve avonturen. Annet en Gerrie, voor een leerzaam jaar in de praktijk. Paul Glasziou, Chris del Mar, Mieke van Driel and Carina Doyle for an expierence 'on the Goldy' that I will never forget. Hugo voor je aangename gezelschap bij de congressen. Nienke, Irene, Ewoud, Corine, Chantal, Judith, Mirjam, Patricia, Rolf, Annette en alle andere kamergenootjes die het werk op het Julius Centrum opgevrolijkt hebben. De leuke groep aiotho's die huisartsgeneeskundige bijeenkomsten altijd weer inspirerend maken en die samen hard werken om de basis van de zorg in Nederland naar een (nog) hoger niveau te tillen. Heleen dat je me, ondanks het vreselijke werk wat ik je aangedaan heb, toch niet 'ontvriend' hebt. Petra voor de gezellige koffiebreaks. Christine, Hatim, Suzanne, Marjolein, Wiedse, Femke, Dick, Dorien, Martijn, Willem, Lisa, Evelien, Arjen, Esther, Gijs, Daniel, Birgit, Jaap, Marleen, Arco en Marilette voor jullie vriendschap. Alle 'Good Cyclers' dat ze mij toegelaten hebben in hun geweldige vriendengroep en altijd weer in zijn voor gezelligheid en een mooie fietstocht, Gelati! De leden van Hellas triatlon die me naast mentaal ook fysiek hebben laten pieken. Bouwe Hofstee, Kees van Rietschoten, Saskia van Vugt en alle andere leden van het 'UMC Utrecht dream team' die het afgelopen jaar van prachtige sportieve hoogtepunten hebben voorzien. De weergoden, dat ze me gezegend hebben met slecht weer in de laatste maanden voor dit proefschrift af moest zijn en ten slotte Janneke Laarakkers, dat ze haar bedrijf 'planpuur'. wilde aanwenden om dit proefschrift ook van de buitenkant mooi te maken. Zelfs nu blijven er nog veel mensen over die ik zou willen bedanken. Maar omdat ik wil voorkomen dat mijn dankwoord het langste hoofdstuk van mijn proefschrift wordt moet ik dit stukje echt afronden. Mocht ik hierboven iemand vergeten zijn, dan is dat alleen op papier.

De laatste alinea's van dit proefschrift wil ik graag besteden aan het bedanken van mijn familie.
Ik voel me een rijk mens dat ik onderdeel ben van een familie met zo veel bijzondere mensen die allemaal niet bang zijn geweest om hun eigen weg te zoeken in het leven. Ook Benno, Harriet en Bart, bedankt voor jullie bijdrage aan het levensgeluk van mijn ouders.
Net zo rijk voel ik mij met mijn schoonfamilie. Nooit geweten dat een koude kant zo warm kan zijn. En in het bijzonder mijn schoonouders, schoonzus en zwager. Jan en Julia, bedankt dat jullie mij met zo veel liefde opgenomen hebben in de familie. Ik zal er alles aan doen om jullie dochter en kleinkind(eren?) een gelukkig leven te laten genieten. Kim, Bas, Welles en Nietes, bedankt voor jullie vriendschap, warmte en geknaag.

Lief sussie, bedankt dat je altijd zo dicht bij me bent, ook al ben je vaak ver weg. Het is heel bijzonder dat, ook al zie ik je minder vaak dan ik zou willen, het iedere keer weer zo vertrouwd voelt om bij je te zijn. Dat kan alleen maar met je zusje.. Oh, en sorry dat ik je als klein broertje vroeger zo geterroriseerd heb, ik hoop dat ik dit in mijn latere leven goedgemaakt heb.

En dan mijn ouders. Bedankt voor alles wat jullie me gegeven hebben. Altijd heb ik kunnen terugvallen op het idee dat, wat er ook gebeurt, jullie er voor me zijn. Daarnaast hebben jullie me altijd gestimuleerd om eruit te halen wat er in zit. Uit het leven, uit sport, uit werk, uit alles. Ook dit proefschrift is een resultaat van het doorzettingsvermogen dat ik van jullie geërfd heb. Bedankt voor de basis die jullie me gegeven hebben en voor alle mooie ervaringen die ik door en met jullie in het leven heb opgedaan.

En dat brengt me bij Julia… Tsja, wat kan ik zeggen na afgelopen jaar waarin je alle lange avonden werken en chagrijnige en wanhopige buien met een glimlach slikte en zei *'ach, alles voor het dankwoord'.* Je weet dat ik aan het werk ben aan een vervolg op dit proefschrift, in 4 delen, genaamd 'Dankwoord aan Julia'. Voordat dat af is zal je het nog even moeten doen met de proloog van dit vierluik.
Zonder jou was er van mijn proefschrift helemaal niets terecht gekomen. Jij hebt me geholpen om te relativeren, om af te remmen, om door te zetten, om creatief te zijn, om zo nodig even niet creatief te zijn, om te genieten en om mijn eigen weg te volgen. Bedankt voor de vrijheid die je me geeft om te zijn wie ik ben en om uit het leven te halen wat ik er uit wil halen. Bedankt dat je samen met mij (en over 2 maanden onze ……..) van het leven een feestje wilt maken. Bedankt dat je bent wie je bent en dat je mijn leven zoveel mooier maakt.

Tenslotte wil ik alle zorg- en andere professionals bedanken voor hun rol in de strijd tegen hepatitis C. Door jullie inzet wordt er veel leed voorkomen, enorm bedankt daarvoor.

Curriculum Vitae

Charles Wilhelm Helsper was born on the 9th of March 1980 in Pullman Washington (USA). After graduating from the Atheneum at the 'Bisschop Bekkers College' in Eindhoven and the first year of Health Sciences at Maastricht University, he studied Medicine at Utrecht University. During these studies he developed an interest for both the practice and research of primary care and prevention. To put this interest into practice he combined the GP-specialty training with a PhD programme at the Julius Center for Health Sciences and Primary Care at the Utrecht Medical Center. During this combined programme he also successfully finished a Prestige Master in Epidemiology, worked as a lecturer at the GP specialty training, at Utrecht University and as an invited lecturer at the Centre for Research in Evidence-Based Practice at Bond University (Australia). The PhD programme, of which you are holding the final result, addresses identification strategies for hepatitis C infection from a primary care point of view.

Currently he is working at the Utrecht GP specialty training and Utrecht University, with a main focus on improving the use and education of scientific evidence in primary care practice. Facilitated by the 'future research star award' awarded by the European Society of Primary Care Gastroenterology, he continues his research on hepatitis C with the objective to improve knowledge and awareness of hepatitis C among GPs in Europe.