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HEPATITIS C - PREVALENCE, RISK FACTORS AND IMPLICATIONS FOR SCREENING

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To all who fight the virus

ABSTRACT

Hepatitis C is a blood-borne virus that mainly affects the liver. The infection is often contracted early in life and remains as an asymptomatic slowly progressive disease. The World Health Organization (WHO) has set a goal to eliminate the hepatitis C virus (HCV) infection in 2030 and in order to reach that, anti-HCV screening is encouraged worldwide. In Sweden, treatment of HCV has been shown to be cost-effective, so the question is not if HCV should be treated but rather how those infected should be identified. The aim of this thesis was to study the prevalence, risk factors, and implications for hepatitis C screening in different groups of individuals.

In **paper I** 7,473 individuals were tested for HCV in a screening campaign. We found an anti-HCV prevalence of 1.8% and a prevalence of chronic hepatitis C of 1.4%. The majority were women transfused due to childbirth. Younger patients were significantly more often started on treatment but no correlation between treatment outcome and age at transfusion was found. Screening of individuals with earlier blood transfusion should be continued.

In **paper II** 5,135 individuals, 4,108 pregnant women and 1,027 partners were tested for HCV at antenatal care clinics. We found an anti-HCV prevalence of 0.7% and a prevalence of chronic hepatitis C of 0.4%, in this group of young adults, mean age 30 years. In this study all were both tested for HCV and asked about different risk factors using a questionnaire. Based on our findings, risk factor-based screening at antenatal care clinics can be used to identify HCV infected women and partners who would benefit from subsequent therapy. The most relevant targeted screening model is to ask for previous or ongoing drug use, blood transfusions, origin in a high-prevalence country, and having a partner with HCV infection.

In **paper III** the impact of kidney disease was investigated. Out of 42,522 diagnosed HCV individuals, 1,077 were found to have a concomitant chronic kidney disease (CKD), and 268 required haemodialysis. In the haemodialysis group, 17% of patients were treated for HCV and survival was significantly higher in the treated cohort compared to the untreated. This study demonstrates that patients with HCV have a higher risk of CKD and need for dialysis and that it is possible to treat patients on haemodialysis with interferon and ribavirin with improved survival.

In **paper IV** we model the cost-effectiveness of universal screening of pregnant women compared to risk factor-based screening. This study is based on data from study II, including 4,108 pregnant women. The main finding of this study is that universal screening can be recommended instead of risk factor-based screening for cost-saving reasons in a Swedish setting, as long as the cost for the screening test is below the cost for the time spent on questions about risk factors at the antenatal care clinic.

To conclude, our studies have resulted in an increased knowledge about the prevalence of hepatitis C in Sweden. The screening strategies need to be renewed, with universal screening or improved risk factor-based screening in different groups of the population, including

analysis of cost-effectiveness. To achieve the goal proposed by the WHO we need to identify and treat as many HCV-infected individuals as possible.

LIST OF SCIENTIFIC PAPERS

I. Millbourn C, Psaros Einberg A, Lindh G, Hökeberg I, Fischler B, Lindahl K. **Prevalence and outcome of post-transfusion hepatitis C acquired at different ages and detected in look-back screening.** Scand J Gastroenterol. 2018;53(7):870-5

II. Millbourn C, Lybeck C, Psaros Einberg A, Nordin M, Lindh G, Hökeberg I, Fredlund H, Fischler B, Fadl H, Duberg AS, Lindahl K. **Anti-HCV prevalence and screening for hepatitis C in pregnant women and their partners in Sweden.**
Submitted

III. Soderholm J, Millbourn C, Busch K, Kovamees J, Schvarcz R, Lindahl K, et al. **Higher risk of renal disease in chronic hepatitis C patients: Antiviral therapy survival benefit in patients on hemodialysis.** J Hepatol. 2018;68(5):904-11

IV. Millbourn C, Lybeck C, Duberg AS, Aleman S, Lindahl K, Fadl H, Ryen L. **Universal anti-HCV screening versus risk factor-based screening in pregnancy in Sweden - a cost-effectiveness analysis.**
In manuscript

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
ALT	Alanine aminotransferase
APRI	AST to platelet ratio index
AST	Aspartate aminotransferase
CDC	Centers for Disease Control and Prevention
CHC	Chronic hepatitis C
CI	Confidence interval
CKD	Chronic kidney disease
DAA	Direct-acting antiviral
DU	Drug use
EASL	European Association for the Study of the Liver
ECDC	European Centre for Disease Prevention and Control
ELISA	Enzyme-linked immunosorbent assay
ESLD	End-stage liver disease
ESRD	End-stage renal disease
FIB-4	Fibrosis-4
GUCI	Göteborg University Cirrhosis Index
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HD	Haemodialysis
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
IDSA	Infectious Diseases Society of America
IDU	Injection drug use
IFN	Interferon
INR	International normalized ratio
MSM	Men who have sex with men
MTCT	Mother-to-child transmission

NS5A	Non-structural 5A
NUC	Nucleoside/nucleotide analogue
OR	Odds ratio
PCR	Polymerase chain reaction
PI	Protease inhibitor
PPI	Proton pump inhibitor
PSA	Probabilistic sensitivity analysis
PWID	People who inject drugs
RBV	Ribavirin
RDT	Rapid diagnostic test
RNA	Ribonucleic acid
SIR	Standardized incidence ratio
SMFM	Society for Maternal-Fetal Medicine
SOC	Standard of care
SVR	Sustained virological response
WHO	World Health Organization
WOCA	Women of childbearing age

1 INTRODUCTION

Morbidity and mortality due to hepatitis C virus (HCV) infection continue to increase. Viral hepatitis, including hepatitis B and C, are among the top ten leading causes of mortality in the world. More than 1.3 million individuals die every year due to viral hepatitis (1). The highest prevalence is in Eastern Europe and Central Asia (2). Most recent calculations indicate that about 70 million individuals are infected with chronic hepatitis C in the world (2). In Sweden the prevalence is estimated to be 0.5% but in the population born in the 1950s and 1960s it is estimated at 1% (3). Approximately 40,000 individuals are infected in Sweden and about 1,600 new cases were reported to the Public Health Agency in 2018 (4, 5).

During the last few years, new and more tolerable drugs have been developed with cure rates of >95%. This is one of the greatest medical advances in decades. The World Health Organization (WHO) has set an ambitious goal, "Viral hepatitis Strategy", to eliminate HCV as a major public health threat by 2030. Between 2015 and 2030, the WHO targets include reducing new HCV infections by 90%, the number of deaths caused by HCV by 65%, and increasing the number of eligible persons receiving HCV treatment to 80% (6).

Since most of the infections with HCV are asymptomatic, screening is a tool to identify individuals at risk of liver disease and who might benefit from treatment. To reach the targets of the WHO, different types of screening are needed, as well as safe blood transfusions, safe injections through harm reduction with needle exchange programs, increased number of needles per people who inject drugs (PWID), and treatment is needed to be eligible for all individuals with chronic hepatitis C (CHC).

2 HEPATITIS C

2.1 BACKGROUND

Hepatitis C virus (HCV) is a blood-borne infection discovered in 1989 (7). Reliable diagnostic methods have been available since 1990. Blood donor screening for hepatitis C, by antibody testing, was introduced in Sweden by January 1st 1992. In countries where blood supply screening is or was suboptimal the risk of transmission remains, and also due to poor hygienic practices there is still a risk for iatrogenic spread.

The hepatitis C virus is a small, enveloped RNA virus belonging to the Flaviviridae family, genus Hepacivirus. The hepatitis C virus infects the hepatocytes causing liver disease in humans, including acute or chronic hepatitis, cirrhosis, and hepatocellular carcinoma.

2.2 EPIDEMIOLOGY OF HCV INFECTION

HCV increased in the population in Sweden in the late 1960s and 1970s, as a result of increased injection drug use (IDU) (3). The highest risk of blood transfusion-transmitted HCV infection was between 1970 and 1985, especially if multiple transfusions were given (8). Estimation of the anti-HCV prevalence was performed in 1991, showing a prevalence of 0.1–0.3% in Swedish blood donors, but no recent estimation has been done (9). The prevalence of chronic hepatitis C in Sweden is estimated to be 0.5%, from 0.1% in blood donors up to 4.4% in patients after open heart surgery (10).

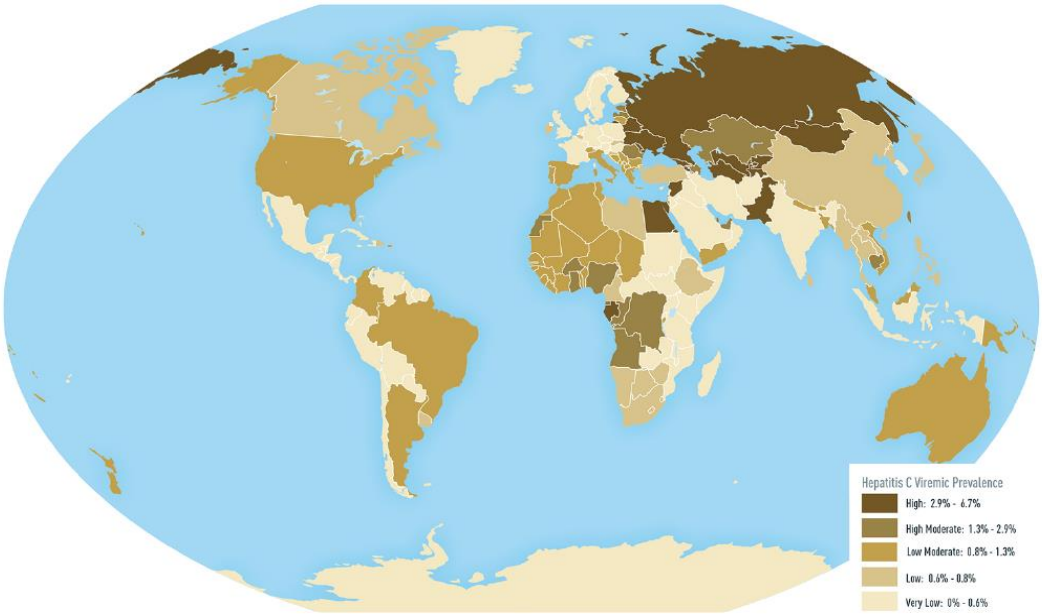

Figure 1 Estimated viraemic HCV prevalence in 2015 Source: Centers for Disease Control and Prevention. CDC Yellow Book 2020: Health Information for International Travel. New York: Oxford University Press; 2017. The Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol. 2017 Mar;2(3):161-76. https://doi.org/10.1016/S2468-1253(16)30181-9.

In 2010 the WHO established a document listing 46 different countries with an anti-HCV prevalence higher than 3% (11). Egypt has the highest prevalence in the world due to nationwide mass anti-schistosomal treatment campaigns with injections almost exclusively using unsterilized and shared syringes and needles. This represents the largest ever nosocomial spread of blood-borne infection (12). A large study in the Nile Delta in 1996 found an anti-HCV prevalence of 24% and viraemic HCV prevalence of 15% among 3,999 examined individuals, with a prevalence in adults >40% (13).

Populations at increased risk of HCV infection include:

- people who inject drugs (PWID)
- recipients of infected blood products (in Sweden before 1992)
- children born to mothers infected with HCV
- men who have sex with men (MSM)
- people with HIV infection
- prisoners or previously incarcerated persons
- dialysis patients
- unexplained elevation of ALT or AST

Due to European Association for the Study of the Liver (EASL) guidelines, screening strategies for HCV infection should be defined within national plans based on the local epidemiology of HCV infection (14).

Injection drug use (IDU) is presently the most common route of transmission in Sweden. Over 80% of injection drug users have antibodies against HCV, whereof 75% have detectable HCV RNA, which is higher compared to what is reported from other parts of the world (15-17). A systematic review of global HCV infection published in 2017 estimated the prevalence among PWID in the United States to be 53% (18).

Other routes of transmission are blood transfusion before 1992 and vertical transmission from mother to child (19, 20). In one meta-analysis the estimated risk of mother-to-child transmission (MTCT) was 5.8%, and it is the primary route of paediatric HCV infection (21). High viral load and co-infection with HIV are the main risk factors for MTCT.

The risk of transmission from sexual contacts is not really known. Studies have reported extremely low risk or even null within heterosexual couples (22, 23). The risk increases for individuals who have more than one sex partner, among men who have sex with men (MSM), co-infection with another sexually transmitted disease, or are infected with HIV.

There is no risk of infection from urine or sweat from an infected individual and there is no transmission of hepatitis C virus through food or water. This means that regular contact and living with someone who has the virus is not a risk. This means that no one should be excluded from work or school because of hepatitis C (24).

Less than 50% of chronically infected adults in the United States are reported to be aware of their diagnosis and the rate is even lower among children (25). In Sweden some 80% are estimated to be aware of their diagnosis, but self-reported HCV status differs from the actual status in many cases both in positive and negative individuals (26). A Swedish study of 1,500 PWID showed that the awareness of having HCV or not was lacking in a large segment of individuals in this group (16).

In Stockholm, during 2018, 364 men and 180 women were newly reported with HCV. The majority were 20-49 years old. The transmission route was reported in 287 individuals and the distribution was 67% IDU, 8% blood or blood products, 5% heterosexual and 3% homosexual transmission (27).

2.3 DIAGNOSIS OF HCV INFECTION

Anti-HCV, HCV RNA, HCV antigen

Hepatitis C infection is diagnosed using an antibody test performed with ELISA technique. The incubation period for hepatitis C is 1-3(6) months but anti-HCV can be detected as soon as 2-12 weeks after transmission in immunocompetent individuals. To diagnose chronic infection a positive antibody test should be followed by a confirmatory PCR test detecting HCV RNA. In non-immunocompetent individuals the seroconversion can be delayed. HCV RNA can be detected as soon as one week after transmission and is therefore a preferably used diagnostic tool in non-immunocompetent individuals. HCV antigen in serum or plasma is a cost-effective marker of HCV replication and is often performed in low- and middle-income areas (14).

Rapid diagnostic test

Rapid diagnostic test (RDT) for anti-HCV have advantages in special settings since the individual receives the answer immediately and the contact with the patient is not lost during the waiting period for the test result. RDT can use serum or plasma, but there are even easier tests using capillary blood or oral fluid (28).

Plasma viral load, genotype

In Sweden today, when the diagnosis of chronic hepatitis C is established, tests for plasma viral load and genotype are performed. HCV genotype should be determined before initiating therapy because it affects the choice and duration of treatment.

There are seven different genotypes (29). In Sweden genotype 1a and genotype 3a are most common, 35% and 31% respectively followed by genotype 2 with 17%, while only 6% have genotype 1b (30). Genotype 3 is relatively more frequent among individuals infected by injection drug use. In a study on HCV infection among childhood cancer survivors in Stockholm, Sweden, a high proportion of genotype 2 was found (31). This can be explained

by genotype 2 being the most frequent genotype among blood donors with HCV infection acquired by previous blood transfusion, suggesting that this genotype used to be more common among blood donors in the 1970s and 1980s.

In Sweden the distribution of genotypes differs from other parts of the world, with a lower frequency of genotype 1 and a higher frequency of genotype 3. Genotype 1 is the most common HCV genotype in the United States, accounting for approximately 70% of prevalent cases (32, 33). The reasons for the different distribution of genotypes in Sweden, compared with other countries is unknown, but could be due to a relatively recent introduction of HCV into the population, or a different pattern of transmission.

2.4 EVALUATION OF FIBROSIS STAGE

Evaluation of the fibrosis stage is recommended to be performed in all patients with chronic HCV infection. Previously, liver biopsy was mandatory to evaluate the grade of inflammation and the fibrosis stage. During the last ten years this procedure has to a great extent been replaced by non-invasive liver elasticity measurement (34-36). The method mostly used in Sweden is by FibroScan® and the result is obtained in kilo Pascal (kPa). Using liver elasticity measurement, the absence of fibrosis as well as the presence of cirrhosis can be diagnosed with reasonably high accuracy. Non-invasive liver elasticity measurement has some limitations such as obesity, high ALT levels, or post-prandial testing (14).

To evaluate the function of the liver, chemical blood samples including ALT, albumin, prothrombin-INR and platelet count are performed. Biochemical markers are used in different risk scores such as Göteborg University Cirrhosis Index (GUCI) score, aspartate aminotransferase (AST) to platelet ratio index (APRI) and fibrosis-4 (FIB-4) (37-39).

Using a combination of validated blood biomarkers and liver elasticity measurement together will provide a sufficient estimate (40).

Both liver biopsy and non-invasive fibrosis evaluations utilize the same protocols of fibrosis stages suggested by Batts and Ludwig or Metavir (41, 42), F0 corresponding to normal liver histology, F1 is mild portal fibrosis, F2 periportal fibrosis, F3 bridging fibrosis and F4 cirrhosis. However, liver biopsy is still the best method to differentiate fibrosis stage F2 and F3 (43).

The severity of the disease in cirrhotic patients should also be evaluated according to the Child-Pugh scoring system, based on bilirubin, albumin, prothrombin-INR and the presence of ascites or hepatic encephalopathy. The stages are divided into Child-Pugh A (compensated cirrhosis), B and C (different levels of decompensation) (44).

Those patients found to have cirrhosis should be included in hepatocellular carcinoma (HCC) surveillance (43). Ultrasound, as a screening method, should be done every six months to identify focal lesions in the liver. If the elasticity measure is above 20 kPa and platelet count

below 150 ($x10^9$/L) the evaluation should also include gastrointestinal endoscopy to check for oesophageal varices.

2.5 HEPATITIS C THE INFECTION

The incubation period is about 7 (2-26) weeks, but only about 15-20% of those with acute hepatitis C infection develop symptoms, consisting of fatigue, abdominal pain, poor appetite, or jaundice (45-47).

Approximately 15-25% of people who are infected with HCV clear the infection spontaneously without therapy and do not develop chronic infection. The mechanism for this is not fully understood. There are studies showing clearance in as many as 45% of infected infants and young women (48, 49). Thus, younger age at the time of infection, female gender and patients who do develop symptoms such as jaundice have a higher likelihood of spontaneous viral clearance than do asymptomatic patients (47). However, an estimated 75-85% of those infected with HCV develop a chronic infection (50, 51).

Usually the progression to advanced liver disease is very slow (52, 53). However, approximately 20% of those with chronic HCV progress to cirrhosis within 20 years from onset of infection, a proportion which tends to increase with age (54).

When cirrhosis has occurred the individual has an elevated risk for complications such as liver decompensation including portal hypertension with oesophageal varices, ascites, and hepatic encephalopathy. Cirrhosis is also associated with an increased risk of developing hepatocellular carcinoma (HCC) with a yearly risk of 3-4% (55). HCV is a leading cause of HCC worldwide and the morbidity and mortality from HCV-associated HCC is increasing in many countries, especially in high-income areas (14). In Sweden in 2018, 244 individuals died from HCC, with any etiology (56). After successful treatment with interferon (INF) and ribavirin the yearly risk for HCC decreased to 1% in cirrhotic patients (43).

Chronic HCV infection with complications used to be a common indication for liver transplantation in Sweden. In 2011, 150 liver transplantations were done, of which about 25% were because of HCV (57, 58). After the introduction of new antiviral therapy in 2014 the proportion of HCV infection among liver transplant recipients has decreased to 3-4% in 2019. The development of HCV-related liver disease is accelerated in liver transplant recipients without effective antiviral treatment and approximately one-third of them develop cirrhosis in the new liver within 5 years (14).

2.6 TREATMENT OF HCV INFECTION

For many years the standard of care (SOC) therapy for hepatitis C consisted of pegylated interferon (IFN), administered once weekly together with daily oral ribavirin (RBV) for 24 to 48 weeks, sometimes extended to 72 weeks (59).

In individuals with HCV genotype 2 or 3 this therapy was quite successful but in patients infected with HCV genotype 1 or 4, only half of treated individuals achieved sustained virological response (SVR), defined as negative HCV RNA 24 or 48 weeks after end of treatment (60, 61).

This treatment was associated with severe side effects (62). Many patients had to stop the treatment because of unbearable side effects and only a few individuals could go on working during the treatment period. For interferon the most common side effects are flu-like symptoms such as fatigue, fever, chills, headache and muscle ache, depression and psychosis, and for ribavirin anaemia, dry skin, rash or eczema. Several groups of patients with co-morbidities were therefore excluded from treatment because of increased risk of side effects. Individuals with ongoing IDU were also excluded. Patients with cirrhosis had a high risk of liver-related complications and had a lower treatment response rate. In Sweden, during this period about 1,000 patients were treated annually, with a total of 10,000-15,000 patients treated with an estimated 40-50% cure rate (61, 63, 64).

In 2011 the first generation direct-acting antivirals (DAA), telaprevir and boceprevir, were approved. With these the treatment was more effective but some patients had severe side effects and severe adverse events (65, 66).

Since 2014 several new agents have been introduced that are more effective and more tolerable. Different combinations of protease inhibitors (PI), NS5A inhibitors and nucleoside analogues (NUC) are used. The new generation DAA has few contraindications and few side effects such as mild headache and nausea. Discontinuations due to adverse events are very few (67). There are some interactions to consider before starting the treatment, for example anti-coagulants, statins, proton pump inhibitors (PPI) and anti-epileptics. The treatment is given orally, 1-3 tablets daily, for eight or twelve weeks. Treatment with new DAA is easy, safe and well tolerated and has a cure rate of >95%, defined as negative HCV RNA 12 weeks after the end of treatment (43).

Before initiating treatment, an individual pre-treatment evaluation is performed including viral load, genotype, estimation of liver fibrosis, tests for HBV and HIV, checking for drug-drug interaction and considering compliance.

Treatment regimens including a protease inhibitor (PI) should not be used in patients with Child-Pugh B or C decompensated cirrhosis or in patients with previous episodes of decompensation. In patients with cirrhosis, HCC-surveillance should be continued even after the patient has achieved SVR because the risk for HCC will only be reduced. With the older

treatment the yearly risk reduced from 5 to 1% but with the new DAA it is not yet well known (68).

Neither natural clearing of the virus or successful treatment make an individual immune to hepatitis C, all individuals can be re-infected with HCV.

The production cost of DAAs is low but in many high- and upper middle-income countries the treatment remains expensive. Due to the introduction of generic versions the price is much lower in some low-income countries.

2.7 COST-EFFECTIVENESS

Worldwide, an increasing number of patients with cirrhosis will develop end-stage liver disease (ESLD) and HCC. With early treatment disease progression can be avoided. Early treatment for hepatitis C is argued to be highly cost-effective when compared to treatment initiated at advanced stages of disease. There are a large number of patients in need of treatment and early treatment would permit the use of shorter treatment and will reduce the cost of treating each patient.

A systematic review showed evidence of economic benefit for screening populations such as birth cohorts, drug users, and high-risk populations (69). Recently a study at a London centre showed that routine antenatal screening can be cost-effective (70). The prevalence among pregnant women doubled in the United States from 2009 to 2014 and a study from January 2019 concluded that universal screening for HCV among pregnant women is cost-effective and should be recommended nationally (71). In Sweden treatment of HCV has been shown to be cost-effective and since January 2018 there are no restriction for antiviral treatment regardless of fibrosis stage and for example ongoing IDU (72).

2.8 ACTION FOR ELIMINATION

There is a remarkable lack of global awareness and action to avoid and combat the disease. On World Hepatitis Day which take place yearly on the 28th of July the WHO draws attention to the major importance of viral hepatitis in public health. According to the WHO, in 2015, of the 70 million individuals living with HCV infection only 20% (14 million) were aware of their diagnosis. Only 7.4% of those diagnosed (1.1 million) were started on treatment. Of those started on treatment, about half received DAAs. Much more needs to be done to achieve the target by 2030.

There are some positive examples of countries working hard towards elimination. For example, Egypt has introduced a national plan and program for managing HCV, which has been successful so far in treating a large number of patients, with the aim of achieving disease control (73).

India has used generic treatment which has enabled antiviral treatment at a lower cost (74).

Iceland started a national program in January 2016, including universal access to DAA for all individuals with chronic HCV, especially PWID and patients with advanced liver disease. They also intensified the work with harm reduction and improved linkage to care (75).

Ten years ago, Scotland started a national scale-up of interventions on hepatitis C among PWID. The conclusion was that most of the decline in HCV incidence in Scotland between 2008 and 2015 was because of the increase of opioid substitution therapy and needle and syringe provision due to government strategies on HCV and drugs (76).

In Sweden a national plan is currently lacking but is underway. There are projects ongoing to trace previously identified positive individuals, to treat PWID and individuals on opioid substitution therapy and to treat incarcerated individuals (77).

Many more countries are working on the development of national hepatitis elimination strategies heading for expanding prevention, screening, and treatment, resulting in a more rapid decline in the total number of patients with viraemic infections.

3 HEPATITIS C AND PREGNANCY

In Sweden there are few reports on anti-HCV prevalence in pregnant women. In a study from Gothenburg an anti-HCV prevalence of 0.8% in 1994 was found (78). A study in a London centre found the same prevalence (79). In different European countries the anti-HCV prevalence is reported to be 0.4-5.2% (80). In the United States the reported prevalence is between 1-2.5% but up to 8% in some states (81-83). The prevalence among pregnant women doubled from 2009 to 2014 in the United States and 29,000 pregnant women with HCV give birth to 1,700 infected neonates every year (84, 85). Worldwide the prevalence is reported to be up to 8% (86, 87).

The epidemiology of hepatitis C has changed from previously being an infection mostly in older patients to now affecting younger people, including women of childbearing age (WOCA), one explanation being the reports from the United States of a tremendous increase in IDU in young adults and teenagers (25, 85). The latest American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) guidelines recommend universal screening of pregnant women (88). Their advice is motivated by this change in epidemiology, and the need of change of obstetrical practices such as avoiding foetal scalp monitoring, prolonged rupture of membranes if known HCV, the introduction of highly effective antiviral treatment after delivery and early identification of infants at risk (89).

Interferon (INF) sometimes with severe side effects and ribavirin with its teratogenic potential are no longer used as treatment for HCV in adults in Sweden. Currently, treatment for hepatitis C cannot be initiating until after delivery. However, effective therapy after delivery provides benefits for subsequent pregnancies, in one study 23% of the women had multiple pregnancies over the three years of the period of the study and treatment after delivery eliminated MTCT risk in future pregnancies (25, 90).

The first small phase I study with new direct-acting antivirals (DAA) during pregnancy has just been completed but the results are pending (91). If DAA would be proven safe during pregnancy, women can be treated during eight to twelve weeks in late pregnancy prior to delivery and the risk of MTCT would most probably be eliminated and the newborns will not need to be followed.

While waiting for the results from ongoing studies of antiviral treatment during pregnancy it is possible to treat children as young as three years old with different combinations of therapy (92-94). However, current Swedish guidelines recommend DAA treatment from the age of 12 years.

After the implementation of universal testing of blood products, transmission from mother to child became the leading source of HCV infection in children. In one meta-analysis the estimated risk of transmission was shown to be 5.8% (21). Delivery by caesarean section is not associated with a lower risk of transmission and is not recommended (95). In addition, there are no recommendations against breastfeeding (96, 97). An earlier delivery of a child

infected perinatally with HCV does not increase the risk of transmission in subsequent pregnancies of the same infected mother (98).

Children born to HCV positive mothers should be tested for anti-HCV at the age of 18 months. Up until that time-point detected anti-HCV can come from the mother. If diagnosis is of interest at a younger age, before the child reaches 18 months, testing for HCV RNA can be performed. HCV RNA testing should then be repeated at a subsequent visit, independent of the initial HCV RNA test result (97, 99).

Pregnancy represents a unique time during which young, otherwise healthy adults may actively engage in medical care. Many of these women are hard to reach for testing and follow-up often because of drug abuse. However, the compliance of pregnant women is often good and in many countries there are special health insurances during pregnancy.

4 HEPATITIS C AND RENAL DISEASE

Hepatitis C virus infection affects many organs, above all the liver but also the kidneys. Patients with HCV have a higher risk of chronic kidney disease and end-stage renal disease (ESRD), and less survival of kidney grafts after transplantation (100). HCV can also be a complication of kidney disease because of earlier transmission within dialysis units. In the early 1990s, once diagnostic testing for HCV became available a high prevalence of hepatitis C virus (HCV) in the chronic kidney disease (CKD) population was recognized. Still, in 2013 the prevalence of HCV in Swedish dialysis patients was 3-4%, compared to the estimated general prevalence of 0.5%. An even higher prevalence, 7.7% was found in a multicentre survey in France, and it seems to be associated with the time on haemodialysis (101). Given these findings it is important to screen HCV patients for kidney disease and the other way around, CKD for HCV. Screening for HCV is recommended on initiation of haemodialysis or at transfer to a new dialysis facility or modality (102).

HCV-positive CKD patients should be evaluated for therapy (103). With the earlier available treatment with interferon and ribavirin only few CKD patients, especially if on haemodialysis, were treated because of the toxicity of the combination. After an HCV-infected patient had undergone kidney transplantation, IFN-based treatments were not recommended owing to the high risk of graft rejection. The new DAAs are effective, well-tolerated, and only on occasion need dose reductions in CKD patients. Kidney Disease Improving Global Outcomes (KDIGO) recommend that the choice of regimen should be based on HCV genotype, prior treatment history, drug–drug interactions, glomerular filtration rate (GFR), fibrosis stage, liver transplant candidacy, and comorbidities (102).

Patients with CKD stage V (GFR <15 (ml/min/1,73 m2)) should be evaluated for kidney transplantation, regardless of HCV status. All kidney transplant candidates with HCV should be evaluated for DAA-based therapy, before or after transplantation. Survival is shown to be greater in kidney transplant recipients compared to those remaining on dialysis (104). Survival of the graft is decreased in HCV positive patients. However, with the introduction of DAA, the question is when to start HCV therapy in relationship to transplantation (105). In patients with decompensated cirrhosis it is preferred to do a combined liver-kidney transplantation and postpone treatment. Some centres have started to transplant kidney allografts from HCV-positive donors due to a long waiting list. This improves the chances for transplantation and treatment can be initiated after the transplantation. This procedure needs a written informed consent from the patient (102).

5 AIMS

The overall aim of this thesis was to study the prevalence, risk factors and implications for hepatitis C screening in different groups of individuals.

5.1 SPECIFIC AIMS

- To investigate the anti-HCV prevalence in subjects receiving blood transfusions in Stockholm and to study what effect age at transfusion has on liver disease and proportion who achieved SVR (Paper I).
- To investigate anti-HCV prevalence in pregnant women in two different Swedish counties and to study if general screening at antenatal care clinics could identify undiagnosed HCV-infections in both pregnant women and their partners (Paper II).
- To describe the Swedish HCV patients with CKD and those undergoing HD and to investigate the impact of IFN-based treatment on survival in HCV positive patients on HD (Paper III).
- To evaluate cost-effectiveness of universal anti-HCV screening compared to risk factor-based screening in pregnant women (Paper IV).

6 MATERIALS AND METHODS

6.1 PATIENTS AND STUDY DESIGN

6.1.1 Paper I

In this single centre retrospective study in Stockholm County, 7,473 individuals were tested for anti-HCV. This was part of a national screening campaign in Sweden in 2008-2010. Subjects were informed through media and encouraged to perform anti-HCV testing at their local health care center if they had received or thought that they had received blood transfusions during the period of 1965-91. The campaign specifically targeted three high-risk groups, including individuals who during childhood had been at risk for blood transfusion due to heart surgery, cancer treatment or neonatal care. All diagnosed with chronic HCV, positive anti-HCV and HCV RNA, were referred to the Department of Infectious Diseases at Karolinska University Hospital for follow-up. Inclusion criterion was blood transfusion as the most likely mode of HCV transmission, exclusion criterion was ongoing or a history of drug use. The HCV RNA positive individuals were divided into two different age groups, young and adults, at the time for the blood transfusions. Data on age at transfusion, age at HCV diagnosis, genotype, viral load, fibrosis score, liver histology and antiviral treatment was recorded.

6.1.2 Paper II

In this cross-sectional study anti-HCV prevalence in pregnant women and their partners was studied in two different counties in Sweden: Örebro and Stockholm. At their first visit at the antenatal care clinic the pregnant woman and her partner were offered anti-HCV screening. The study individuals completed a form about characteristics and risk factors for HCV. In total 5,135 individuals were tested and of these 4,108 were pregnant women.

6.1.3 Paper III

In this retrospective registry-based study 42,522 individuals positive for hepatitis C were followed and checked for the development of CKD. Patients were identified for chronic hepatitis C and CKD according to the International Classification of Diseases (ICD-10) in the nationwide Swedish inpatient day care surgery (1997–2013) and non-primary outpatient care (2001–2013) patient registries. Haemodialysis was defined using the code for this procedure at least once in the record of the patient. For each patient, up to five comparators without hepatitis C, matched on age/sex/place of residency were drawn from the general population at the time of diagnosis. Follow-up started at the date when hepatitis C was diagnosed and all patients and controls were followed from birth until death, emigration, or the date of December 31st, 2013, whichever came first.

6.1.4 Paper IV

In this study, we modelled the cost-effectiveness of universal screening of pregnant women compared to different levels of risk factor-based screening in Sweden. The model is based on

data from study II including 4,108 pregnant women. The differences in cost divided by the differences in effect between universal screening and risk factor-based screening was estimated, the incremental cost-effectiveness ratio (ICER) (106).

$$ICER = \frac{Cost_{universal\ screening} - Cost_{risk\ factor-based\ screening}}{HCV\ cases\ identified_{universal\ screening} - HCV\ cases\ identified_{risk\ factor-based\ screening}}$$

To acknowledge uncertainty, sensitivity analysis was performed, both one-way sensitivity analysis and probabilistic sensitivity analysis (PSA) by means of Monte Carlo (107).

6.2 METHODS

6.2.1 Virological methods

Screening serology of anti-HCV was performed using Abbott Architect Anti-HCV (Abbott Laboratories, Abbott Park, IL, USA), confirmed with Inno-LIA HCV Score (Fujirebio Europe, Technologiepark 6, Gent, Belgium) or Chiron RIBA HCV 3.0. HCV RNA levels were measured by MagNa Pure LC/COBAS TaqMan System or AmpliPrep/COBAS TaqMan System (Roche Diagnostics AB). HCV genotype was performed using an in-house method (108).

6.2.2 Biochemical methods

All biochemical tests were performed using routine methods at the local laboratories. We calculated fibrosis index using the Gothenburg University Cirrhosis index (GUCI) score: (AST (µkat/L) / TopNormal AST (µkat/L)) * prothrombin-INR * 100 / platelet count ($x10^9$/L) (37, 109).

6.2.3 Histological methods

In order to estimate the fibrosis stage both liver biopsy and non-invasive transient elastography were used. Liver biopsies were classified according to Batts and Ludvig. Liver stiffness by transient elastography was done using FibroScan® (Echosens, Paris, France).

6.2.4 Questionnaire

In paper II a questionnaire was used regarding the characteristics of the study subjects and risk factors for HCV such as DU, blood transfusions, partner with HCV, country of origin, tattoo or piercing and previous hospital care. The questionnaire was handed to the study subjects by the midwife at the antenatal care clinics.

6.2.5 National registers

In paper II the National Pregnancy Register (110) was used to compare the characteristics of the study population and the background population.

In paper III several registers were used, the National Patient Register, Cancer Register, Prescribed Drug Register, Total Population Register and Causes of Death Register. The coverage in these registers is high due to the universal use of personal identification numbers in Sweden.

6.2.6 HCV treatment

The standard of care treatment for HCV until December 2013 was pegylated interferon and ribavirin. Since January 2014 DAA has been the standard of care treatment in Sweden.

6.2.7 Statistical methods

For statistical significance Pearson, Fishers exact or independent t-test was used. In study III we used both a univariate regression analysis and presented as odds ratios (OR) and a multivariate regression model. Hazard ratios (HR) was calculated using a Cox Regression model.

All reported p-values were 2-sided and a p-value of <0.05 was considered statistically significant.

Statistical analysis was performed with STATA software 13 (Stata Corp. College Station, TX, USA) Paper I, SPSS (version 25, 21; IBM Corp, Armonk, NY, USA) Paper II and III, TreeAge Pro 2019, R2 (TreeAge Software, Williamstown, MA, USA) Paper IV.

6.2.8 Ethics

All studies were performed in accordance to the Helsinki declaration and were approved by The Regional Ethical Review Board in Stockholm, Dnr 2011/1372-31/3 (Paper I), Dnr 2013/1035-31/3, 2018/342-32 (Paper II, IV) and Dnr 2014/746-31 (Paper III).

7 RESULTS AND DISCUSSION

7.1 PAPER I

7.1.1 Prevalence, characteristics and treatment outcome

Out of 7,473, 134 (1.8%) tested individuals were anti-HCV positive and 102 were HCV RNA positive resulting in a prevalence of chronic hepatitis C of 1.4%. The rate of advanced liver damage was 18% (10/56). The majority of the infected were women transfused due to pregnancy and delivery. Only nine individuals were from the targeted risk groups. There was a wide range of age at diagnosis and the oldest one was 92 years old.

Patients younger than 19 years of age at transfusion were significantly more often started on antiviral treatment compared to adult patients, 65% vs 29% p<.001. However, the oldest treated patient who achieved SVR was 65 years old. Those infected with genotype 2 and 3 had a higher rate of SVR, 82% versus 45% p<.018. No significant correlation was found between treatment outcome and gender or age at transfusion.

7.1.2 Blood transfusion as risk factor for hepatitis C

IDU increased in Sweden in the 1960s and 1970s, and as a result of that, hepatitis C, at that time called non-A non-B (NANB) hepatitis, became more prevalent in the 1970s (3, 111). When blood donor screening was introduced in 1991, 0.1-0.5% of Swedish blood donors had antibodies to HCV (9, 112, 113). In 2006 the number of blood donors in Sweden was 250,000 and 20 of them were tested positive for anti-HCV in the normal screening (5). Today, 3% of the population between the ages of 18-75 years donate blood at least once a year (114).

7.1.3 Screening strategies after blood transfusion

Most regions in Sweden conducted this campaign only through information to the population (115). In Stockholm the information was via newspapers, websites and posters at the local health care centres. Active tracing was used in just a few areas of Sweden and reviewing old records was considered time consuming and expensive and often not possible due to incomplete records.

Since a relatively low number of individuals were tested in Stockholm during this campaign and especially those from the three targeted risk groups, new strategies of finding these individuals are needed. In a combined retrospective register based and prospective screening study, adults who during childhood ($n = 686$) had been treated for malignancy in Stockholm before 1992, were contacted resulting in testing of 235 patients and of these 11 were HCV-RNA positive (31).

As a result of the campaign the recommendations for testing today also include women transfused during pregnancy or delivery since this was a group not tested and lacks follow-up after blood transfusion (116).

Unawareness of previous blood transfusion during childhood is common. Children have a higher lifetime risk of HCV-related complications than adults.

7.1.4 Discussion

In 2007, the National Board of Health and Welfare in Sweden started this targeted campaign for screening of hepatitis C in recipients of blood transfusion (8). At that point it was considered relevant to identify blood recipients of potentially hepatitis C-infected blood because of better knowledge of complications of hepatitis C and more effective treatment.

Before initiating the screening campaign the number of individuals from the specific targeted risk groups in Stockholm were estimated to be about 12,000 individuals, some 2,000 due to heart surgery, 600 to cancer treatment and 9,000 due to neonatal care, respectively (117). It was expected that 5% would be anti-HCV positive and of these 75% HCV RNA positive and that one third would have known HCV. The campaign in Stockholm resulted in only nine newly diagnosed individuals from the defined paediatric risk groups instead of the estimated 270.

However, the campaign did find a total of 102 infected individuals of whom a great proportion, during the study period and after, successfully have been treated and achieved SVR.

The distribution of men and women differed in this study with more women infected. Approximately 60-70% are men in most epidemiological studies which is also reflected in the yearly reports from the Public Health Agency (5). Median age at diagnosis in this study is higher, since 49% of patients were diagnosed at an age of 61 years or older, compared to about 40 in the above yearly reports.

Since many individuals are not aware of previous blood transfusion and since most individuals with hepatitis C are without symptoms we need screening. The screening of recipients of blood transfusions during 2007-2010 in Sweden shows that with increased testing of risk groups we can identify more cases (5). New screening strategies at antenatal care clinics can be seen as a continuation of the national campaign in a place where young asymptomatic adults come into contact with healthcare.

7.2 PAPER II AND IV

7.2.1 Prevalence, risk factors and screening

In Paper II we found 34 (0.7%) anti-HCV positive individuals (25 women, 9 partners), and of these 10 were previously unknown. Risk factors for transmission were DU (n=27), partner with known HCV (n=24) and origin from a country outside Sweden (n=8). Chronic infection, with positive HCV RNA, was detected in 23 individuals (0.4%). The most effective risk factor-based screening model for pregnant women in this study was to ask for DU, blood

transfusions, born in a high-prevalence country, and having a partner with HCV, resulting in 538 (13%) pregnant women tested with 96% sensitivity, 87% specificity.

The main finding of Paper IV is that universal screening can be recommended instead of risk factor-based screening for cost-saving reasons in a Swedish setting. This will be of advantage as long as the cost of screening tests is lower than the cost for the time needed for the midwife at the antenatal care clinic to interview pregnant women about possible risk factors.

7.2.2 Universal versus risk factor-based screening

In paper II both universal screening and a questionnaire concerning risk factors for HCV such as DU, previous blood transfusion, ever having a partner with known HCV, country of origin, tattoo/piercing and previous hospital care was used. The study subjects were also asked for known former HCV status. Based on the answers, different combinations of risk factors were investigated and checked for how many individuals needed to be tested with the different combinations, and the specificity and sensitivity were calculated. The conclusion was that risk factor-based screening at antenatal care clinics can be used to identify HCV-infected women and partners who need follow-up and therapy.

7.2.3 Cost-effectiveness of universal versus risk factor-based screening

In Sweden, treatment of HCV has been shown to be cost-effective, so the question is not if HCV should be treated but rather how those infected should be identified at the lowest possible cost (72). In paper II we concluded that risk factor-based screening is possible and in paper IV we added cost-effective analysis. To make this calculation the cost of the screening test must be compared to the cost of the time used by the midwife to ask several questions about possible risk factors. In paper IV we show that as long as the cost for the screening test is below the time needed for interviewing the pregnant women, universal screening is a dominant strategy and will save costs.

7.2.4 Discussion

Pregnant women are already routinely screened for several infectious diseases, but not yet for HCV infection (118).

We need better screening strategies in different groups of the population. Screening at antenatal care clinics is one possibility to reach many young individuals, both pregnant women and their partners. Both improved risk factor-based screening and universal screening are possible alternatives.

Universal screening for hepatitis C is not at present recommended in pregnant women by the European Centre for Disease Prevention and Control (ECDC), Centers for Disease Control and Prevention (CDC) or Society for Maternal-Fetal Medicine (SMFM) (89, 119, 120). In the latest EASL guidelines from 2018 screening of HCV in pregnancy is not commented on, but the latest American Association for the Study of Liver Diseases (AASLD)/Infectious

Diseases Society of America (IDSA) guidelines recommend universal screening of pregnant women (14, 88).

Ever since 2010, the Act on Pregnant Woman Care in Poland have implemented anti-HCV screening for all pregnant women. Before 2010, 9 % were diagnosed with unknown risk factors and after 2010, 46.1 % were diagnosed without risk factors. That large group, without risk factors, can only be detected through universal screening examinations (90).

In paper II it was shown that it is possible to use risk factor-based screening resulting in both high sensitivity and specificity. However, risk factor-based screening is not optimal since providers often do not ask about risk factors and individuals do not tell. In paper IV it was shown that due to cost-effectiveness universal screening is preferred as long as the cost of the screening test is lower than the cost for asking about risk factors.

7.3 PAPER III

7.3.1 Chronic kidney disease in Swedish HCV patients

Between 2001 and 2013, 2.5% (n=1,077) of the Swedish HCV patients had a reported CKD diagnosis. This resulted in a higher incidence of CKD diagnosis within the HCV cohort than expected when comparing with the group of matched comparators, 3.84 cases per 1,000 person-years in the HCV cohort versus 0.97 cases per 1,000 person-years in the comparator cohort, resulting in a SIR of 4.0 (95% CI 3.7-4.2).

7.3.2 Hepatitis C and haemodialysis

In total 268 HCV patients had ≥1 haemodialysis (HD) procedure code during the study period. Almost all HD patients had kidney failure diagnosis. Younger age at initiating of HD, receiving either kidney transplantation or HCV treatment, or getting an acute kidney failure diagnosis was significantly associated with survival in haemodialysis patients when analysing using a univariate regression model. These four factors also independently predicted survival when using a multivariate regression analysis.

The annual prevalence of HCV among haemodialysis patients in Sweden was between 3% and 4% for the years 2010 through 2013. The overall chronic HCV prevalence in Sweden is estimated to be around 0.5%. Of the HD patients 17% (45/268) had received HCV treatment, 60% (27/45) of these received HCV treatment after initiating HD. In the group of haemodialysis patients started on treatment 24% (11/45) died during the study period compared to 56% (124/223) in the untreated group.

7.3.3 HCV treatment in haemodialysis patients

During the study period SOC was still IFN-based treatment. In this study, 17% (45/268) of patients on haemodialysis had received HCV treatment. Treatment before or after start of

haemodialysis did not affect survival, but those receiving treatment had a significant better outcome.

Standard treatment today consists of elbasvir/grazoprevir or glecaprevir/piprentasvir. Both combinations can be used regardless of renal function, including haemodialysis patients (121, 122). These treatments have been shown to be well tolerated and with high cure rates.

7.3.4 Discussion

Morbidity and mortality in haemodialysis patients and kidney transplant recipients are affected by hepatitis C and liver complications (123). The prevalence of HCV in haemodialysis units in high-income countries is declining, but remains high, as high as 70 %, in some low-income countries (124).

In our study the treatment rate in haemodialysis patients was high, 17%. Treatment with interferon and ribavirin in patients on haemodialysis, as in other groups of patients is associated with a high risk for adverse events and side effects, and the dosing schedules have been complicated (125). In an international observational study only 1% of haemodialysis patients with HCV had received treatment, as long as the SOC treatment was interferon and ribavirin (126).

HCV is a risk factor for transition from chronic kidney disease to end-stage renal disease (ESRD) and the presence of anti-HCV in haemodialysis patients is a risk factor for death, due to increased risk of cirrhosis and HCC in this specific group of patients (127, 128). It is also shown that haemodialysis can have a negative impact on the course of HCV infection.

The survival rate for HCV-infected renal transplant recipients is better than in HCV-infected haemodialysis patients remaining on transplant waiting lists (129). An explanation for this can be that well-functioning renal allografts is decreasing uremic toxins.

Early diagnosis, treatment of HCV infection with new effective DAA treatment, and kidney transplantation prevents complications and reduces mortality. At present all haemodialysis patients should be considered for receiving treatment to cure the HCV infection.

8 CONCLUSION AND FUTURE ASPECTS

These four studies include different groups of individuals with either increased risk for hepatitis C or who should benefit from extended screening.

The anti-HCV prevalence in the nationwide screening campaign in Stockholm, among individuals who have received blood transfusion, was higher than in other parts of Sweden. In the campaign only few individuals from the three targeted risk groups were identified. However, during the study period and after, 59 individuals achieved SVR after treatment, decreasing their risk of liver complications.

Hepatitis C is a global health problem and since most infections are asymptomatic, universal or risk factor-based screening is needed. Screening at antenatal care clinics can be used for diagnosis of HCV-infection in both pregnant women and partners. Those found to be HCV positive can be linked to care for follow-up and effective treatment.

There is an increased risk of chronic kidney disease and dialysis dependency in patients with hepatitis C. In our study antiviral treatment improved survival of patients with hepatitis C on haemodialysis. After the introduction of DAA, all haemodialysis patients should be considered for receiving treatment to cure the HCV infection.

To analyze cost-effectiveness of universal screening versus risk factor-based screening the cost for the screening test and the cost for the time needed to ask questions about risk factors must be included. Under the base-case assumptions, universal screening is a dominant strategy, saving costs while giving equal or higher effectiveness. This will be the case as long as the cost of screening tests is below the cost for the time used in maternal care to interview pregnant women about possible risk factors.

There is a need for more data on the total burden of hepatitis C in Sweden. The consequences of hepatitis C are extensive both for the individual and for the society. To prevent the prevalence of HCV from continuing to increase worldwide a global effort is needed. The best public health strategy is identification and treatment of as many individuals with chronic hepatitis as possible. With the new drugs treatment is simple and should be adopted aggressively in order to reduce the prevalence.

Screening and treatment of PWID is not included in this thesis. To eliminate HCV, as proposed by the WHO, increased screening and treatment in this group is crucial. There is a need for new guidelines about how often PWID should be screened, with which method and further knowledge of reinfections must be obtained.

In the future, rapid diagnostic tests are needed as well as adequate tests for identification of viraemic individuals which will facilitate linkage to care and treatment. Since pan-genotypic treatment is available, genotype analysis would be optional or perhaps excluded. Measurement of liver elasticity will not be necessary in young individuals with a short duration of intravenous drug use and short duration of disease because of a low probability of

advanced disease. In these subpopulations eight weeks of treatment is enough to achieve SVR.

To conclude, since hepatitis C often is asymptomatic a great proportion of individuals with chronic hepatitis C are unaware of their infection. To be able to identify these individuals, extended screening of different groups at risk is required and then correct calculation of prevalence and incidence can be done. To be able to reach the worldwide target in 2030 there is a need to further increase screening and treatment for hepatitis C.

9 SAMMANFATTNING PÅ SVENSKA

Hepatit C virus smittar via blodet och infekterar levern. Många smittas tidigt i livet och utvecklar ofta en kronisk men asymtomatisk infektion som efter hand kan leda till leverfibros, skrumplever och levercancer. Eftersom majoriteten inte har några symtom kan man bära på infektionen utan att veta om det. Idag är den vanligaste smittvägen via intravenöst missbruk då man delar nålar eller annan icke-steril utrustning. Barn kan smittas från modern under graviditet och förlossning. Tidigare var även blodtransfusion en risk för smitta men sedan 1992 kontrolleras allt blod i Sverige. Sedan 2014 finns effektiv behandling mot hepatit C, denna består av 1 till 3 tabletter dagligen i 8 till 12 veckor. Behandlingen har väldigt få biverkningar och över 95% av behandlade patienter läker ut. Världshälsoorganisationen (WHO) har satt som mål att eliminera hepatit C till år 2030. För att uppnå det målet behövs ökad kunskap om förekomsten av hepatit C och våra metoder för screening måste förnyas. Syftet med den här avhandlingen var att studera förekomsten av hepatit C i olika grupper, riskfaktorer för att smittas och utvärdera olika metoder för screening.

I första studien fann vi en högre förekomst av hepatit C hos individer i Stockholm som fått blodtransfusion före 1992 jämfört med allmänheten. Den var också högre jämfört med motsvarande grupp i hela Sverige. Studien visade också att yngre individer oftare påbörjade behandling mot hepatit C men vi fann ingen skillnad i utläkningsfrekvens beroende på vid vilken ålder som blodtransfusionen givits.

I andra studien testades gravida och deras partners för hepatit C på barnmorskemottagningar i Örebro och Stockholm. Andelen infekterade av hepatit C var något högre jämfört med tidigare uppskattning av förekomsten i Sveriges befolkning. Vid screening baserad på riskfaktorer fann vi att den bästa kombinationen är att fråga om aktuellt eller tidigare drogmissbruk, tidigare blodtransfusion, ursprung i land med känd högre förekomst av hepatit C och tidigare eller aktuell partner med känd hepatit C. Vår slutsats är att denna metod för screening är möjlig för att kunna diagnostisera både gravida och deras partner och därmed kunna erbjuda blivande föräldrar med hepatit C vård och behandling.

I tredje studien användes flera olika register för att beräkna andelen patienter med hepatit C som också drabbats av njursvikt och behov av dialys. Vi studerade hur många av de med dialys som fick behandling mot hepatit C och dödligheten hos de behandlade jämfört med de obehandlade. Vi fann att patienter med hepatit C i högre utsträckning, jämfört med en kontrollgrupp utan hepatit C, utvecklade njursvikt och behov av dialys. Andelen dialyspatienter, i den här studien, som behandlades var högre än i andra delar av världen och de hade en bättre överlevnad.

Fjärde studien bygger på våra resultat i studie II. Med en kostnadseffektivitetsanalys jämfördes kostnad för provtagning av hepatit C hos alla gravida med testning av en del av de gravida baserat på frågor om olika riskfaktorer med ökad risk för blodsmitta. Huvudfyndet i studien är att så länge priset för blodprovet för hepatit C är lägre än kostnaden för den

arbetstid som krävs av barnmorskan att ställa frågor kring faktorer med ökad risk för blodsmitta så är generell testning kostnadseffektiv.

Sammanfattningsvis visar våra resultat att förekomsten av hepatit C i de studerade grupperna är något högre än hos allmänheten, screening baserat på riskfaktorer hos gravida är möjligt men provtagning av alla gravida kan vara mer kostnadseffektivt. För att nå det uppsatta målet från WHO om eliminering behöver vi ha nya riktlinjer för vilka som ska provtas för att vi ska kunna diagnostisera och behandla så många som möjligt mot hepatit C.

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