Hepatitis C in two general practices in Flanders, Belgium: is there a need to reconsider current screening recommendations?

Ruth Botterman, Universiteit Gent

Promotor: Dr. P. Boeckxstaens, Universiteit Gent

Co-promotoren: Prof. Dr. A. Derese, Dr. T. Van Der Paelt, Dr. X. Verhelst, Prof. Dr. H. Van Vlierberghe; Universiteit Gent

Praktijkopleider: Dr. E. Vandedrinck

Master of Family Medicine

Masterproef Huisartsgeneeskunde

ABSTRACT

Achtergrond

Wereldwijd is het hepatitis C Virus (HCV) een belangrijke oorzaak van acute en chronische leverziekten (bv. cirrose en hepatocellulair carcinoom) met jaarlijks zo'n 672 000 doden. De aandoening vormt een belangrijke uitdaging voor de volksgezondheid, vergelijkbaar met andere veel voorkomende overdraagbare ziekten zoals HIV, tuberculose en malaria. Het bestrijden van virale hepatitis C is onlangs op de 2030 WHO agenda voor duurzame ontwikkeling geplaatst. Een van de doelstellingen voor het uitroeien van hepatitis C, is het diagnosticeren van 90% van de geïnfecteerde patiënten. In België focussen de huidige screeningsaanbevelingen op risicogroepen. We zien echter dat 50% van de geïnfecteerde patiënten in België niet op de hoogte zijn van hun diagnose.
Deze studie onderzoekt de prevalentie van een HCV infectie bij patiënten die twee huisartspraktijken in Vlaanderen, België bezochten. De meest voorkomende risicofactoren worden besproken en er wordt onderzocht of de huidige screeningsaanbevelingen in Vlaanderen toepasbaar blijven.

Methode

Er werd een cross-sectionele studie uitgevoerd in een plattelandspraktijk in Lendelede en in een stedelijk wijkgezondheidscentrum in Gent, België. Patiënten die naar de praktijk kwamen voor opvolging van een chronische aandoening of voor een acuut probleem, en die een bloedafname nodig hadden, werden uitgenodigd om hun HCV status te laten testen. De beschreven meest voorkomende risico factoren werden geregistreerd. Wanneer een patiënt een positief HCV antilichaam had, werd een PCR analyse uitgevoerd om het HCV RNA te bepalen.

Resultaten

Er werden 1112 patiënten geïncludeerd in de studie. Negentien patiënten waren HCV AL positief (1.71%) en zeven waren HCV RNA positief (0.63%). Vijf patiënten kenden hun infectie status niet. IV drug gebruik en afkomstig zijn van een niet-Belgisch, laag-endemisch land, zijn significant geassocieerd met een positief HCV AL. Bij vier van de 19 HCV AL positieve patiënten werden geen geregistreerde risicofactoren gevonden.

Conclusie

Deze studie bevestigt de onderschatting van HCV infecties in Vlaanderen. Dit ligt zowel aan het gegeven dat niet alle risico groepen gescreend worden als aan het gegeven dat er positieve patiënten worden gevonden buiten de risico groepen. Deze resultaten evenals de recente vooruitgang in behandelopties en hun terugbetaling, verantwoorden het herzien van de huidige screeningsaanbevelingen voor HCV in Vlaanderen. Verder onderzoek is nodig om te bepalen wat de meest effectieve screeningsstrategie zou zijn.

ABSTRACT

Background and aims

Hepatitis C virus (HCV) is a major cause of acute and chronic liver disease (e.g. cirrhosis and hepatocellular carcinoma). In Belgium, screening recommendations focus on risk groups. However, it is estimated that 50% of the infected patients are undiagnosed. This study assessed the prevalence of HCV in patients visiting two general practices in Flanders, Belgium. We revealed the associated risk factors and explored whether the current recommendations for HCV screening need to be reconsidered.

Methods

A cross-sectional study in a non-urban practice in Lendelede and an urban community health center in Ghent, Belgium was performed. Patients for whom a blood test was required, were recruited for HCV screening. A patient survey assessed the associated risk factors.

Results

There were 1112 patients included in the study. Nineteen patients were HCV Ab positive (1.71%) and seven were HCV RNA positive (0.63%). Five patients were unaware of their status. Using IV drugs and being born in non-Belgian low-endemic country are significantly associated with HCV Ab positivity. Four of the 19 HCV Ab positive patients didn't meet any of the registered risk factors.

Conclusion

This study confirms the problem of underdiagnosis of HCV, which is both related to the fact that not all risk groups are being screened and to the fact that patients are identified beyond the risk groups. These results, as well as the current changes in treatment options and their reimbursement, justify a reconsideration of the current recommendations for screening of HCV. To develop the most effective screening strategy in Flanders, further research is necessary.

Introduction

Globally, hepatitis C virus (HCV) is a major cause of acute and chronic liver disease (e.g. cirrhosis and hepatocellular carcinoma), leading to an estimated 672 000 liver-related deaths annually . Recently the treatment of chronic HCV infection has improved considerably with the development of highly effective, well-tolerated oral direct-acting antiviral (DAA) treatment regimens (1). Along with the growing recognition of the burden of disease and the opportunities for action, hepatitis C moves on the health and development priority list. In 2016 the World Health Organization (WHO) put the aim to combat viral hepatitis on the 2030 Agenda for Sustainable Development (2). The goal is the elimination of HCV infection as a public health threat, with elimination defined as a 90% reduction of new chronic infections and a 65% reduction in mortality compared with the 2015 baseline. This requires diagnosing 90% of those infected and treating 80% of those diagnosed (3, 4).

One of the main barriers to tackle HCV is that many patients are unaware of their infection status. The lack of reliable estimates of the undiagnosed population, has become one of the main challenges to scale-up screening and prevention programs for HCV (5). Correct prevalence information is important to install a feasible screening strategy and it can also help to estimate the global cost to cure infected patients (5). In Belgium, the most recent study on the seroprevalence of HCV antibodies (0.87%) dates back to 1997 (6). Currently, experts estimate that around 70 000 people in Belgium are infected with HCV, of which only 50% is aware (7). Detecting the undiagnosed population starts with an appropriate screening strategy. Screening for hepatitis C by making use of HCV-antibodies meets the Wilson and Jungner criteria for feasibility of screening (8), presented in box 1. An important issue however, is to detect the most appropriate and cost-efficient group to screen. Globally, several different screening strategies are on the rise. The USA and Canada for example, have since 2012, advocated one-time HCV screening 'baby boomers' (those born between 1945 and 1965), representing the bulk of the HCV prevalence (9, 10). In France, a population-based one-time simultaneous HCV, HBV and HIV testing in men aged 18-60 is recommended (11, 12). Furthermore a total population screening in France was recently detected as the most effective screening strategy for HCV (12, 13). These strategies aren't applicable to other countries with a different HCV epidemiological profile. In Belgium, the 'Federaal Kenniscentrum voor Gezondheid' (KCE Report 173A 2011) and the Belgian Association for the Study of the Liver (BASL) advice risk-based screening (see box 2) (14). A recent study conducted in two Emergency Departments (ED) in Belgium (Ghent and Hasselt) however showed that this strategy is insufficient (5, 15).
Our aim is to study the seroprevalence of HCV infection in patients visiting two general practices in Flanders, Belgium, in order to assess the need to reconsider the current risk-based screening for HCV in our country.

1. The condition sought should be an **important health problem**.
2. There should be **an accepted treatment** for patients with recognized disease.
3. **Facilities for diagnosis and treatment** should be available.
4. There should be a **recognizable latent or early symptomatic stage**.
5. There should be a **suitable test or examination**.
6. The test should be **acceptable to the population**.
7. The **natural history** of the condition, including development from latent to declared disease, should be adequately **understood**.
8. There should be an **agreed policy on whom to treat as patients**.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should **be economically balanced** in relation to possible expenditure on medical care as a whole.
10. **Case-finding** should be a **continuing** process and not a "once and for all" project.

BOX 1. Wilson and Jungner classic screening criteria (8)

- Persons with one of the following medical interventions in Belgium before 01.07.1990, date of introduction of anti-HCV tests on blood and derived or related products: blood transfusion, major surgery (cardiovascular, digestive, pulmonary, gynaecology-obstetrics, orthopedic, etc.), stay on intensive care, including neonatal intensive care, difficult birth, gastrointestinal bleeding, tissue, cell or organ transplant
- Dialysis patients
- Persons who use intravenous or intranasal drugs
- Children of mothers who are HIV positive
- Sexual partners and cohabiting patients with a hepatitis C infection
- Persons who have tattoos or a piercing, or acupuncture, in which no use was made of single use material or personal material
- Persons who received medical care in a high HCV prevalence country (Southeast Asia, Middle East, Africa, South America)
- Persons with an unexplained increase in transaminases
- Patients who are HIV-positive or HIV-positive
- Persons with a cleared asthenia
- Persons with a history of unexplained jaundice

BOX 2. The KCE high risk groups (14)

Research questions

1. What is the seroprevalence of HCV infection in two general practices in Flanders and what are the differences between an urban and a non-urban practice?

2. What are the associated risk factors?

3. Is the current screening strategy still applicable?

Materials and methods

Study design

In this article we discuss a duo-centric cross-sectional opportunistic study of general practices in Flanders, Belgium. The data of a non-urban general practice 'De Vierschaar' in Lendelede was collected from 01/11/2016 until 31/10/2017 and published in 2019 by Acta Gastroenterologica Belgica (16). In the community health center 'WGC Botermarkt' in Ghent, an urban general practice, data was collected from 09/07/2018 until 15/11/2018.
All patients between 18 and 100 years of age, in need of a blood sample for various reasons, could be included. Patients were recruited by doctors and nursing staff. There were no exclusion criteria. In both practices a positive HCV antibody test was confirmed using PCR to determine the viral load (HCV RNA). Patients characteristics and certain risk factors were registered.
Both studies were approved by the medical ethics committees of Ghent University and good clinical practice guidelines were followed.

Setting

In Lendelede, a non-urban practice with around 4000 registered patients from more or less 15 different nationalities, the study was performed by five general practitioners (16). The study in Ghent was performed in a community health center with around 6500 registered patients from 89 different nationalities. In this practice, ten general practitioners and ten nurses performed the study.

Definition of risk factors

The two studies are performed on regional level, with each their own study protocol, which caused a difference in registered patient characteristics and risk factors.
In Lendelede, the registered characteristics in all included patients were age, gender, origin, drug use and MSM (men who had sex with man). Only patients who had a positive HCV Ab were asked to fill in a full questionnaire regarding the risk factors (KCE Report 173A 2011) (see box 2). In Ghent, the following characteristics were registered within all patients: age, gender, origin and some of the high risk factors (IV drug use, blood transfusion before 1990, having a piercing or tattoos).
The variable 'origin' was divided in three subcategories: Belgium, non-Belgian low endemic countries and non-Belgian high endemic countries (considering as high endemic the countries mentioned in the KCE Report 173 A 2011: South East-Asia, Middle East, Africa, South-America).
The variable 'birth cohort' was divided in two subcategories: patients born between 1945-1965, seen as the baby boom cohort (17) and patients born outside this cohort.
The other variables were binominal.
In former studies the association between the baby boom generation and HCV infection varies among countries (5, 17), therefore we created an extra variable by combining origin and birth cohort.
Before 1990 transfused blood wasn't tested on HCV, which implies that baby boomers who had received a blood transfusion in that period are at higher risk for a HCV infection (14). Considering this, another extra variable combining blood transfusion before 1990 and birth cohort was created.

Data Analysis

All statistical analyses were performed with SPSS statistics. The two-sided Fisher's exact test was used to identify risk factors associated with HCV Ab positivity. To study the influence within the independent risk factors, multiple logistic regression models are used. Results were considered statistically significant at the 0.05 level. Nagelkerke's R^2 was applied to evaluate the model fit.

Results

HCV seroprevalence and population characteristics

In Table 1 the population characteristics (gender, mean age and risk factors) of the two studies are presented.

In total, from the 1112 patients visiting the two general practices in Flanders screened, 19 patient were HCV Ab positive (1.71%); of them 7 had a positive HCV RNA (0.63%). In this group of HCV Ab positive patients, we found 4 patients (21%) who didn't score positive on any of the studied risk factors. Five patients (26.3%) were unaware of their viral status.

In the non-urban practice 'De Vierschaar' in Lendelede 560 patients were included (for the population characteristics see Table 1). Five patients (0.89%) had a positive HCV AL test. Three of them (0.54%) had a chronic active hepatitis C infection (HCV RNA positive). Only one of those three knew her infection status and was already in treatment. The other two HCV RNA positive patients and the two chronic non active HCV positive patients had been undiagnosed so far.

In the urban community health center 'WGC Botermarkt' in Ghent 552 patients were included (for the population characteristics see Table 1). Fourteen (2.5%) of them had a positive HCV Ab test. From those, 10 were HCV RNA negative: 8 had been treated successfully and 2 cleared spontaneously. The 4 HCV RNA positive patients (0.72%) were not yet eligible for therapy in September 2018. Among the 14 positive HCV AL patients only one who was not aware of his status, the patient had a spontaneously cleared HCV infection.

Risk factors for hepatitis C infection

In Table 2 we provide the results of the bivariate analysis of the risk factors associated with HCV positivity in family practices in Flanders, Belgium. Using IV drugs ($p = 0.000$ OR 41.37 CI: 10.94-156.20) and being born in a non-Belgian low-endemic country ($p = 0.002$ OR 5.77 CI: 2.14-15.57) are significantly associated with HCV infection. The patients tested in the non-urban practice had a significantly lower probability for HCV Ab positivity compared to the patients tested in the urban practice ($p < 0.05$ OR 0.35 CI: 0.12-0.97). Furthermore patients of Belgian origin were significant less likely to have a HCV infection ($p < 0.05$ OR 0.37 CI: 0.15-0.91). There is no correlation for gender and birth cohort.

In Table 3 we show the logistic regression model A. Using IV drugs ($p = 0.000$ OR 46.93 CI: 9.18-239.93) and being born in a non-Belgian low-endemic country ($p = 0.006$ OR 6.23 CI: 1.69-22.90) remained significantly associated with HCV infection. Controlled for practice and gender, patients born in the baby boom cohort are less likely to be HCV Ab positive ($p < 0.05$ OR 0.25 CI: 0.08-0.77). Due to the different composition of risk factors in the two practices, 'practice' is no longer significant in the regression model.

Table 4 presents model B with the relation between the combined variable birth cohort by origin and HCV Ab positivity, controlled for IV drug use, practice and gender. Patients born outside the baby boom cohort in a non-Belgian low-endemic country are more likely to have a HCV infection compared to baby boom patients from another origin ($p = 0.000$ OR 20.28 CI: 3.85-106.83). IV drug use remains a significant risk factor for HCV Ab positivity ($p = 0.000$ OR 42.59 CI: 8.59-211.25). Interpreting the Nagelkerke R^2, fitting of model B (Nagelkerke R^2 0.201) was slightly better than model A (Nagelkerke R^2 0.189). Both coefficients however prove that the models still leave an important part of the variability unexplained.

For the following risk factors the association with HCV Ab positivity could not be studied due to the differences in data registration over the practices: having tattoos or piercings, MSM and blood transfusion before 1990.

Having had a blood transfusion before 1990 is seen as an imported risk factor (14), therefore we studied the association with HCV infection for the urban patients (for the non-urban patients this data was not registered) (results are presented in Table 5-7 in the appendix). In a bivariate analysis, this risk factor is significantly associated with HCV Ab positivity ($p = 0.001$ OR 14.32 CI: 3.86-53.12). In this same analysis, birth cohort, gender, origin, IV drugs use and tattoos and piercings were analyzed. For the baby boom patients the HCV Ab positivity is significantly less likely compared to those patients being born outside that period ($p < 0.05$ OR 0.30 CI: 0.10-0.87). In the logistic regression model C, only having had a blood transfusion before 1990 remained significantly associated ($p = 0.000$ OR 20.46 CI: 3.90-107.41) with HCV infection when controlled for birth cohort, gender, origin, IV drug use and having tattoos or piercings.
We built a logistic regression model D to analyze the relation between the combined variable birth cohort by blood transfusion and HCV Ab positivity, controlled for the same variables. Patients from the baby boom cohort who had received a blood transfusion are more likely to have a HCV infection compared to patients without a blood transfusion of both birth cohorts ($p < 0.05$ OR 0.07 CI: 0.01-0.65).
Note that IV drug use and non-Belgian low- endemic country origin were also significant risk factors for HCV Ab positivity ($p < 0.05$) in every model studied on this group of urban patients.

	Total	Urban – Non urban		HCV Ab+	Urban – Non urban	
		Ghent	Lendelede		Ghent	Lendelede
N=	**1112**	552	560	**19**	14	5
Gender						
- Female	**647**	306	341	**11**	8	3
- Male	**465**	246	219	**12**	6	6
Age range	**18-92**	18-90	18-92	**27-89**	34-79	27-89
Mean age	**48.5**	46	51	**56**	56	56
Patients born between 1945-1965	**327**	140	187	**9**	8	1
Amount of different birth countries	**66**	50	16	**7**	6	1
HCV high prevalence countries	**42**	34	8	**3**	3	0
Patients with a non-Belgian origin	**273**	257	16	**9**	9	0
Bloodtransfusion < 1990	*	23	*	**6**	4	2
IV drugs	**11**	11	0	**4**	4	0
Piercing tattoo	*	153	*	*	2	*
MSM	*	*	10	*	*	1
No risk factors	*	*	*	**4**	2	1
HCV RNA +	**9**	6	3	**9**	6	3
Healed after treatment	**6**	6	0	**6**	6	0
Spontaneously cleared	**4**	2	2	**4**	2	2
Newly diagnosed	**5**	1	4	**5**	1	4

TABLE 1. HCV Ab positive patient characteristics and risk factors (*this data is missing)

Riskfactors	HCV Ab+ (total)	P-value	OR	95%CI
Birthcohort				
- Other	12 (554)	0.26		
- 1955-175	7 (558)		0.57	0.22-1.47
Gender				
- Male	8 (465)	1.00		
- Female	11 (647)		0.99	0.39-2.48
Practice location				
- City	14 (552)	**0.04**		
- Village	6 (560)		**0.35**	0.12-0.97
Origin				
- High endemic countries	3 (192)	1.00	0.90	0.26-3.11
- Low endemic countries	6 (87)	**0.002**	**5.77**	2.13-15.57
- Belgian	10 (833)	**0.03**	**0.37**	0.15-0.91
Drug use IV				
- No	15 (1099)	**0.000**		
- Yes	4 (13)		**41.37**	10.94-156.42

TABLE 2. Univariate influence (Fisher's exact tests) of risk factors on HCV Ab prevalence

	S.E.	P-value	OR	95%CI
(Constant)	0.61	0.00	0.02	
Babyboom (ref. other)	0.57	**0.02**	0.25	0.08-0.77
Origin (ref. belg)				
- Low-endemic	0.66	**0.006**	**6.23**	1.69-22.90
- High-endemic	0.75	0.49	1.68	0.38-7.35
Practice (ref. urban)	0.67	0.30	0.50	0.11-1.84
Drug IV (ref. no)	0.83	**0.000**	**46.93**	9.18-239.93
Gender (ref. men)	0.50	0.84	1.11	0.41-2.95

TABLE 3. Logistic regression Model A (Nagelkerke R^2: 0.189)

	S.E.	P-value	OR	95%CI
(Constant)	0.61	0.00	0.02	
Babyboom and Belgian		**0.005**		
- Babyboom and low- endemic	0.97	0.31	2.65	0.40-17.70
- Babyboom and high-endemic	1.17	0.69	0.62	0.63-6.19
- No babyboom and Belgian	0.73	0.42	1.81	0.43-7.58
- No babyboom and low-endemic	0.85	**0.000**	**20.28**	3.85-106.83
- No babyboom and high-endemic	0.94	0.06	5.98	0.94-38.05
Practice (ref. urban)	0.66	0.39	0.57	0.16-2.07
Drug IV (ref. no)	0.83	**0.000**	**42.59**	8.59-211.25
Gender (ref. men)	0.50	0.77	1.16	0.43-3.14

TABLE 4. Logistic regression Model B (Nagelkerke R^2: 0.201)

Discussion

Summary of results

The overall prevalence of HCV Ab (1.71%) identified in this study is higher than what has been shown in earlier trials in the general Belgian population (0.87%) (6, 14). This result highlights the underestimation of HCV in Flanders, Belgium. The difference in prevalence between an urban and non-urban practice, respectively 2.5% and 0.89%, can mostly be explained by the different prevalence of risk factors. With five patients (26.3%) being unaware of their infection status, even when they met the risk factors, the study shows that certain patients remain undiagnosed and the current screening strategy isn't always well applied. A central point of attention is that we found more undiagnosed patients within the population with a lower prevalence of risk factors.
Analyzing the risk factors, IV drug use is associated with HCV infection in both practices, which corresponds with previous research (14). Another significant risk factor were patients born in a non-Belgian low-endemic country, this in contrast to other studies who described only high endemic patients at risk. An explanation can be that some of the infected patients in Ghent were born in East-European countries, which aren't mentioned as highly endemic. This results show that we found HCV positive cases outside the KCE-recommended risk groups.
Since only patients of the baby boom cohort who also had a blood transfusion before 1990, are more likely to have a HCV infection, the results show that only screening patients born in the baby boom cohort isn't a conclusive strategy to use in Flanders. This has been also demonstrated in other recent prevalence studies (5, 15).

Comparing to the international literature

Total prevalence

Literature shows that prevalence data for HCV is limited and varies widely trough different regional studies performed in Belgium and Europe (3).
Recent studies gathered the various prevalence data. In Belgium a review shows a HCV prevalence rate of 0.99 % [(95%CI): 0.64- 1.42%] (18). In Europe, the estimated prevalence of HCV in the European Union (EU) and Economic Area (EEA) is 1.1% (95% CI: 0.9- 1.4) (19). The prevalence range widely, from 0.4% to 3.5%, with countries in Southern and Eastern Europe being most affected (20). Remember that these regions aren't included so far in the high risk countries, mentioned in the KCE report (14).

Significant associated risk factors

The patients at highest risk for a HCV infection vary trough European and Belgian prevalence studies (3-5, 21). Which is seen for example in the different association with the birth cohort in Belgium and Europe (18). Studies in France, Germany and the Netherlands, could not find an effect in a specific birth cohort. Studies in Spain and the Czech Republic, however, did show an association (5). These differences in studies can be explained by differences in study characteristics such as test methods, inclusion criteria of the patients, influence of risk factors and regional observations.
Which also explains the differences identified the two studied practices in Flanders.

International screening strategies

The WHO describes three target groups for screening (2017 testing guidelines) (see appendix) (1):
1. Focused testing in most-affected populations. (Strong recommendation, low quality of evidence)
2. General population testing in settings with a ≥2% or ≥5% HCV antibody seroprevalence in the general population. (Conditional recommendation, low quality of evidence)
3. Birth cohort testing of older persons at higher risk of infection and morbidity within populations that have an overall lower general prevalence. (Conditional recommendation, low quality of evidence).

In Belgium, current recommendations focus on the most-affected populations with KCE and BASL recommending risk-based screening in the health system (14). By applying these correct, three of the five patients who were unaware of their status, would have been detected. France recently updated their screening strategy to a one-time simultaneous HCV, Hepatitis B virus (HBV) and HIV testing in men aged 18-60 and pregnant women in the first trimester (22). The USA and Canada for example, have since 2012, advocated for a one-time HCV screening in patients born between 1945 and 1965 'babyboomers') (9, 10). None of those two strategies would have detected the other two undiagnosed patients.

Strengths and limitations

In this study an opportunistic screening was performed. This is a convenient way to screen in general practices. Patients, from whom a blood test had to be taken, were invited to have their HCV status checked. The test is easy to get, comes with no extra charges or discomfort for the patient. By performing the study in two practices with a different patient epidemiology, the combined result can give a better idea of population dispersion in Flanders. However even within this combined study design, the most vulnerable groups (such as health care avoiders, homeless people, prisoners, certain drug users,..) who are at a greatest risk or who are most affected, are failed to reach.
This may lead to an underestimation in our prevalence results.
On the other hand, the difference in study design and inclusion criteria of the participants between the two practices can be seen as a limitation, because it restricted the possibility for comparing several risk factors.
By screening the group of patients in need of a blood test, we selected only a part of the population, which is a limitation for our study. For reliable epidemiological data, a HCV seroprevalence study on the total healthy population is necessary.
The two studies depended on the good-will and motivation of the nurses and general practitioners to inform the patients about the study and ask them to participate. We are aware that eligible patients who visited one of the practices in the study period may not have been included because of limited consultation time, forgetting to mention the study, … This may have led to unintentional selection bias. Furthermore certain patients were maybe not included because of language barriers; this could have led to a lower inclusion of non-Dutch speaking migrants. Throughout the study we observed a few patients refusing to participate out of fear of a positive result.
In this article we focused on factors which may hinder testing of patients as an important barrier to eradicate HCV infection in Belgium. The WHO report of july 2018 regarding hepatitis C, also mentioned possible barriers to successful linkage to care, treatment and prevention (e.g. a HCV vaccine) (3, 4). To reach the aim of HCV elimination these themes should also be studied in Belgium. An accessible health care model should be developed for all patients who get the HCV diagnosis.

Implications for practice, policy and further research

As mentioned before, HCV infection testing meets the Wilson and Jungner criteria for feasibility of screening (8). When HCV is diagnosed in an early stadium, treatment can be started quickly. This results in a reduction in morbidity and mortality, prevents an evolution towards advanced disease, avoids major treatments, decreases medical costs, improves the chances of survival of the patients and limits the further transmission of hepatitis C (1). Despite these promising benefits, screening also entails negative aspects. A positive test result can lead to anxiety in patients, even though they will not always experience the negative effects of their infection: for example when the infection clears itself or when there is a very slow disease progression. The consequences of a positive test result should always be taken into account and the patients need to be informed about possible treatment options. The patients should always have the option to refuse the screening. Furthermore, screening can lead to false reassurance and after every new risk contact, rescreening should take place.
The observed underdiagnoses of HCV, the current change in treatment options and the recent treatment reimbursement in Belgium (from the first of January 2019 the treatment for hepatitis C will be reimbursed for all infected patients, regardless of the stage of the disease (7)),however, made us look into the current screening strategy in Flanders.
Our results show that the risk-based screening strategy, recommended by the KCE, isn't properly applied today: primary health care workers are overwhelmed by prevention matters and have not acquired HCV-screening as useful and necessary, like they did for other preventive issues. Our study advocates for reconsidering the KCE-recommended strategy: we found HCV+ cases outside the KCE-recommended risk groups. However, the percentages are low: WHO recommends HCV-screening in populations group were the prevalence is >2%, which could be the case in certain population groups identified within our sample.
It is clear that to develop the most effective screening strategy, further research is necessary.

Conclusion

The seroprevalence found in this study (1.71%) can confirm the underestimation of HCV in Flanders, Belgium. The difference in prevalence between an urban and non-urban practice, respectively 2.5% and 0.89%, can mostly be explained by the different prevalence of risk factors. Our results show that the risk-based screening strategy, recommended by the KCE, leads to missing cases of HCV infections. On the other hand, we found HCV positive cases outside the KCE-recommended risk groups. These results, as well as the current change in treatment options and the recent overall treatment reimbursement, justify a reconsidering of the current screening strategy for HCV in Flanders. To develop the most effective screening strategy in Flanders, further research is necessary.

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Appendix

Riskfactors	HCV Ab+ (total)	P-value	OR	95%CI
Birthcohort				
- Other	6 (412)	**0.03**		
- 1955-175	8 (140)		**0.30**	0.10-0.87
Gender				
- Male	6 (246)	1.00		
- Female	8 (306)		1.07	0.37-3.14
Origin				
- High endemic countries (yes)	3 (34)	0.57	0.57	0.15-2.02
- Low endemic countries (yes)	6 (230)	**0.01**	**4.49**	1.52-13.30
- Belgian (yes)	5 (288)	0.28	0.50	0.16-1.50
Drug use IV				
- No	10 (541)	**0.000**		
- Yes	4 (11)		**30.34**	7.64-120.44
Bloodtransfusion <1990 (n=506)				
- No	7 (483)	**0.001**		
- Yes	4 (23)		**14.32**	3.86-53.12
Tattoo/Piercing				
- No	12 (399)	0.37		
- Yes	2 (153)		0.43	0.09-1.93

TABLE 5. Univariate influence (Fisher's exact tests) of risk factors on HCV Ab prevalence in WGC Botermarkt (bivariate analyse)

N = 552	S.E.	P-value	OR	95%CI
(Constant)	0.91	0.00	0.08	
Gender (ref. men)	0.72	0.64	0.72	0.18-2.93
Baby boom (ref. other)	0.77	0.26	0.42	0.09-1.89
Origin (ref. Belgian)		**0.05**		
- Low-endemic	2.30	**0.01**	**9.94**	1.59-62.03
- High-endemic	1.27	0.19	3.56	0.54-23.63
Tattoo/piercing (ref. no)	1.12	0.48	0.45	0.05-4.05
IV drugs (ref. no)	1.05	**0.000**	**57.93**	7.36-456.21
Blood transfusion (ref. no)*	0.77	**0.000**	**20.46**	3.90-107.41

*there are 8.3% (46) missings for this variable

TABLE 6. Logistic Regression Model C HCV Ab WGC Botermarkt (Nagelkerke R^2: 0.328)

N = 552	S.E.	P-value	OR	95%CI
(Constant)	0.91	0.00	0.08	
Gender (ref. men)	1.75	0.47	0.59	0.14-2.52
Babyboom cohort and Bloodtransfusion (BTF)	0.77	**0.001**		
- Babyboom no BTF	1.15	**0.000**	**0.02**	0.00-0.16
- No babyboom with BTF	1.41	0.66	0.54	0.03-8.60
- No babyboom no BTF	1.11	**0.02**	**0.07**	0.01-0.65
Origin (ref. belg)		**0.05**		
- Low-endemic	2.28	**0.01**	**9.80**	1.61-59.56
- High-endemic	1.26	0.18	3.55	0.55-22.83
Tattoo/piercing (ref. no)	1.14	0.52	0.48	0.05-4.47
IV drugs (ref. no)	1.06	**0.000**	**71.42**	8.92-541,73

*there are 8.3% (46) missings for this variable

TABLE 7. Logistic Regression Model D WGC Botermarkt (Nagelkerke R^2 0.129)

Attachments

Approved protocol by the ethical committee

Het aantal besmettingen van hepatitis c is de laatste jaren aan het dalen. Toch weet de helft van de (naar schatting) 100 000 besmette Belgen niet dat ze drager zijn van het virus. Chronische hepatitis C veroorzaakt meestal geen klachten maar kan op lange termijn leiden tot cirrose, een hepatocellulair carcinoom en levertransplantatie.

Deze masterproef wil aanvullend onderzoek doen naar screening van HCV bij alle patiënten ouder dan 18 jaar in een eerstelijnssetting.
Onze beslissing om ook buiten de gekende risicogroepen te screenen is gebaseerd op verschillende overwegingen (zie Van Vlierberghe H, Verhelst X. UZ Letters; mrt-apr-mei 2018: #134):
- Met de nieuwe antivirale middelen is het mogelijk geworden een genezingspercentage van hepatitis C te bereiken van 98% zonder belangrijke bijwerkingen[1]: indien we erin slagen alle hepatitis C-besmette personen te detecteren, bestaat de mogelijkheid om hepatitis tegen 2030 in België uit te roeien; dit is kosteneffectief, omdat vergevorderde stadia van leverfibrose/cirrose, hcc en daarmee gepaard gaande behandelingen (incl.leverrescties en –transplantaties) voorkomen worden
- Screenen kan zich niet beperken tot de risicogroepen: in 2 recente onderzoeken (1 op de spoedafdeling van het UZGent, en 1 in een huisartspraktijk in Lendelede) blijkt dat patiënten drager kunnen zijn zonder het te weten, en zonder dat zij behoren tot een van de risicogroepen
- Ondanks de 2 hierboven vermelde onderzoeken blijft voorlopig onduidelijk hoeveel patiënten in België besmet zijn met het hepatitis C-virus; dit kan maar duidelijk worden als de screening (die reeds wordt aanbevolen) in meerdere, van elkaar verschillende populaties wordt uitgevoerd.

In de hierboven geschetste context is het eenmalig testen van alle patiënten boven de 18 jaar verantwoord, en kan de test o.i. ook verantwoord worden aangerekend aan het riziv Op zich stelt het riziv immers geen voorwaarden voor de terugbetaling van hepatitis c testing. Daarenboven is het volgens het KCE kennisrapport 173A (2012) weinig waarschijnlijk dat de 673 000 anti-hcv testen die elk jaar door de ziekteverzekering in België terugbetaald worden allemaal gericht aangevraagd worden bij de doelpopulaties.

Wijkgezondheidscentrum botermarkt in Ledeberg biedt een interessante setting voor dit onderzoek. In vergelijking met de twee eerdere onderzoeken in Vlaanderen is er een hogere prevalentie van mensen met een migratieachtergrond en van mensen in een precaire leefsituatie. In deze patiëntenpopulatie zijn we er ons van bewust dat de risicofactoren niet altijd gekend zullen zijn door de zorgverstrekker (vb onderrapportering door patiënten gelinkt aan stigma, taalbarrières,…).
Praktisch zal bij elke patiënt die om willekeurige reden een bloedafname dient te ondergaan informed consent gevraagd worden om ook de bepaling van hepatitis c antilichaam uit te voeren. Patiënten zullen bij informed consent ook een vragenlijst krijgen met de belangrijkste risicofactoren. De doelgroep omvat zowel patiënten die komen voor een bloedafname in kader van de opvolging van een chronische aandoening of volgens de geldende preventierichtlijnen, als bloedafnames in het kader van gerichte diagnostische onderzoeken. De extra aanvraag zal voor de patiënt geen extra kost met zich meebrengen aangezien de test tot het standaardpakket behoort voor het basisremgeld. Bij de patiënten die positief testen zal er nog getrapt een bij aanvraag gebeuren om te kijken of het gaat

om een actieve of een doorgemaakte infectie. Deze patiënten zullen telefonisch ingelicht worden en uitgenodigd worden om de diagnose en therapie te bespreken.

De patiënten die als drager van hepatitis c worden geïdentificeerd zullen naar de dienst hepatologie worden doorverwezen; diegenen hiervan met fase 2, 3 of 4 leverfibrose of als co-morbiditeit HIV, nierfalen of hemofilie kunnen reeds een door het riziv terugbetaalde behandeling krijgen.

Tot slot, met dit onderzoek hopen we een beter zicht te krijgen op de prevalentie van HCV in Vlaanderen en de noodzaak tot uitbreiding van de screening. Op deze manier dragen we bij aan good clinical practice omtrent screening naar hepatitis C in Vlaanderen. De HCV-bepaling betekent geen meerkost voor de patiënt. Deze test kan in het licht van recent onderzoek gezien worden als onderdeel van standaardpraktijkvoering en behoort zo tot het riziv-vergoedbaar aanvragenpakket.

Favourable opinion ethical commitee

contact	telefoon	e-mail
Sandra De Paepe Commissie voor medische Ethiek	+32 (0)9 332 26 88	Ethisch.comite@uzgent.be sandra.depaepe@uzgent.be

Ons kenmerk	Uw kenmerk	datum	pagina
2018/0405		24-apr-18	1/2

Betreft :

Advies voor monocentrische studie met als titel:
Screening van Hepatitis C in een wijkgezondheidscentrum in Gent (MaNaMa Ruth Botterman)

Belgisch Registratienummer: B670201836078

* Antwoord onderzoekers via mail dr. R. Botterman dd. 02/04/2018 (ontv. dd. 03/04/2018) op opmerkingen EC dd. 20/03/2018
* (Patiënten)informatie- en toestemmingsformulier (ontv. dd. 03/04/2018)
* Vragenlijst HCV studie (versie 1) (ontv. dd. 03/04/2018)
* Antwoord onderzoekers via mail dr. R. Botterman dd. 12/04/2018 in antwoord op opmerkingen na ontvangst 1ste antwoord dd. 3/04/2018
* Adviesaanvraagformulier - Aangepaste versie (ontv. dd. 12/04/2018)

Advies werd gevraagd door:
Prof. dr. A. DERESE ; Hoofdonderzoeker

ALGEMENE DIRECTIE
Commissie voor Medische Ethiek

VOORZITTER:
Prof.dr. D. Mathys

SECRETARIS
Prof.dr. J. Decruyenaere

STAFMEDEWERKER
Muriel Fouquet
T +32(09) 332 33 35
Sabine Van de Moortele
T +32(09) 332 68 54
Sara De Smet

SECRETARIAAT
Wendy Van de Velde
T +32(09) 332 56 23
Sandra De Paepe
T +32(09) 332 26 88
Ann Heerebeke
T +32(09) 332 22 66
Davine Verbeke
T +32(09) 33222 66

INGANG 75
ROUTE 7522

BOVENVERMELDE DOCUMENTEN WERDEN DOOR HET ETHISCH COMITÉ BEOORDEELD. ER WERD EEN POSITIEF ADVIES GEGEVEN OVER DIT PROTOCOL OP 12/04/2018. INDIEN DE STUDIE NIET WORDT OPGESTART VOOR 12/04/2019, VERVALT HET ADVIES EN MOET HET PROJECT TERUG INGEDIEND WORDEN.

Vooraleer het onderzoek te starten dient contact te worden genomen met Bimetra Clinics (09/332 05 00).

THE ABOVE MENTIONED DOCUMENTS HAVE BEEN REVIEWED BY THE ETHICS COMMITTEE.
A POSITIVE ADVICE WAS GIVEN FOR THIS PROTOCOL ON 12/04/2018. IN CASE THIS STUDY IS NOT STARTED BY 12/04/2019, THIS ADVICE WILL BE NO LONGER VALID AND THE PROJECT MUST BE RESUBMITTED.

Before initiating the study, please contact Bimetra Clinics (09/332 05 00).

DIT ADVIES WORDT OPGENOMEN IN HET VERSLAG VAN DE VERGADERING VAN HET ETHISCH COMITE VAN 17/04/2018

THIS ADVICE WILL APPEAR IN THE PROCEEDINGS OF THE MEETING OF THE ETHICS COMMITTEE OF 17/04/2018

UZ GENT
UNIVERSITEIT GENT
Universitair Ziekenhuis Gent
C. Heymanslaan 10 | B 9000 Gent
www.uzgent.be

- *Het Ethisch Comité werkt volgens 'ICH Good Clinical Practice' - regels*
- *Het Ethisch Comité beklemtoont dat een gunstig advies niet betekent dat het Comité de verantwoordelijkheid voor het onderzoek op zich neemt. Bovendien dient U er over te waken dat Uw mening als betrokken onderzoeker wordt weergegeven in publicaties, rapporten voor de overheid enz., die het resultaat zijn van dit onderzoek.*
- *In het kader van 'Good Clinical Practice' moet de mogelijkheid bestaan dat het farmaceutisch bedrijf en de autoriteiten inzage krijgen van de originele data. In dit verband dienen de onderzoekers erover te waken dat dit gebeurt zonder schending van de privacy van de proefpersonen.*
- *Het Ethisch Comité benadrukt dat het de promotor is die garant dient te staan voor de conformiteit van de anderstalige informatie- en toestemmingsformulieren met de nederlandstalige documenten.*
- *Geen enkele onderzoeker betrokken bij deze studie is lid van het Ethisch Comité.*
- *Alle leden van het Ethisch Comité hebben dit project beoordeeld. (De ledenlijst is bijgevoegd)*

- *The Ethics Committee is organized and operates according to the 'ICH Good Clinical Practice' rules.*
- *The Ethics Committee stresses that approval of a study does not mean that the Committee accepts responsibility for it. Moreover, please keep in mind that your opinion as investigator is presented in the publications, reports to the government, etc., that are a result of this research.*
- *In the framework of 'Good Clinical Practice', the pharmaceutical company and the authorities have the right to inspect the original data. The investigators have to assure that the privacy of the subjects is respected.*
- *The Ethics Committee stresses that it is the responsibility of the promotor to guarantee the conformity of the non-dutch informed consent forms with the dutch documents.*
- *None of the investigators involved in this study is a member of the Ethics Committee.*
- *All members of the Ethics Committee have reviewed this project. (The list of the members is enclosed)*

Namens het Ethisch Comité / On behalf of the Ethics Committee

Prof. dr. D. MATTHYS
Voorzitter / Chairman

CC: De heer T. VERSCHOORE - UZ Gent - Bimetra Clinics
FAGG - Research & Development; Victor Hortaplein 40, postbus 40 1060 Brussel
Universiteit Gent - Faculteit geneeskunde en gezondheidswetenschappen; De Pintelaan 185 9000 Gent