Prospective Study

Emergency department targeted screening for hepatitis C does not improve linkage to care

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Author contributions: Shibolet O, Horowitz N and Katchman H designed the research; Weksler Y and Miller O performed the research; Houri I and Deutsch L analyzed the data; Houri I and Shibolet O wrote the paper; Houri I, Katchman H, Deutsch L and Shibolet O critically reviewed the manuscript.

Supported by an Educational Grant from AbbVie Inc. Israel.

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Abstract

BACKGROUND
Hepatitis C virus (HCV) infection is a leading cause of chronic liver disease worldwide. New treatments for HCV revolutionized management and prompted the world health organization to set the goal of viral elimination by 2030. These developments strengthen the need for HCV screening in order to identify asymptomatic carriers prior to development of chronic liver disease and its complications. Different screening strategies have been attempted, most targeting high-risk populations. Previous studies focusing on patients arriving at emergency departments showed a higher prevalence of HCV compared to the general population.

AIM
To identify previously undiagnosed HCV carriers among high risk emergency room attendees and link them to care for anti-viral treatment.

METHODS
In this single center prospective study, persons visiting the emergency department in an urban hospital were screened by a risk factor-specific questionnaire. The risk factors screened for were exposure to blood products or organ transplantation before 1992; origins from countries with high prevalence of HCV; intravenous drug use; human immunodeficiency virus carriers; men who have sex with men; those born to HCV-infected mothers; prior prison time; and chronic kidney disease. Those with at least one risk factor were tested for HCV by serum for HCV antibodies, a novel oral test from saliva (OraQuick®) or both.

RESULTS
INTRODUCTION

Hepatitis C viral (HCV) infection is a leading cause of chronic liver disease and associated with an increased risk of developing cirrhosis, hepatocellular carcinoma, and liver transplantation worldwide[1,2]. The heavy burden of disease and the recent marked advances in HCV treatment have led the World Health Organization (WHO) to declare a goal of elimination of viral hepatitis as a major public health threat by 2030[3], and to propose that each country develop a strategy to promote prevention and treatment of viral hepatitis. The goals set were a 30% reduction of new cases of chronic hepatitis B virus (HBV) and HCV and a 10% reduction of viral hepatitis-associated deaths by 2020, and by 2030 - a 90% reduction of new cases and a 65% reduction of deaths. Many countries have begun implementing programs to that end[4-6].

In order to achieve these goals, two main obstacles need to be overcome. The first is to identify HCV infected persons, and the second is to link them to care. Globally, less than 5% of viral hepatitis (HBV and HCV) carriers are aware of their diagnosis[7]. A study in the United States showed that 50% of patients diagnosed with HCV were unaware of their status[8]. Therefore, in order to achieve the WHO goals, we need to integrate viral hepatitis testing into routine health policies and define priority populations for screening.

The benefits of early detection of HCV are significant, as timely treatment decreases the risk for all liver-related complications, as well as the potential for virus transmission. Different strategies for identifying these patients have been used[9]. Universal screening was implemented in France and was found to be effective[10,11]. Other screening programs target high-risk populations, as previous studies have shown that 85%-90% of HCV-infected patients had an identifiable risk factor[12,13]. These included people associated with HCV-infected patients had an identifiable risk factor and were tested for HCV. Eighty-four percent of all study participants had at least one risk factor. Eighty-five percent of participants underwent OraQuick® testing, 34% were tested for serum anti-HCV antibodies, and 25% had both tests. 3.1% of patients (17/541) had a positive result, compared to local population incidence of 1.96%. Of these, 82% were people who inject drugs (current or former), and 64% served time in prison. One patient had a negative HCV-RNA, and two patients died from non-HCV related reasons. On review of past medical records, 12 patients were found to have been previously diagnosed with HCV but were unaware of their carrier status. At 1-year follow-up none of the remaining 14 patients had completed HCV-RNA testing, visited a hepatology clinic or received anti-viral treatment.

CONCLUSION

Targeted high-risk screening in the emergency department identified undiagnosed and untreated HCV carriers, but did not improve treatment rates. Other strategies need to be developed to improve linkage to care in high risk populations.

Key words: Screening; Emergency departments; Israel; Saliva; Hepatitis C; Liver
who inject drugs (PWID), recipients of blood transfusion before 1992 and abnormally elevated liver enzymes. In addition to these risk factors there are population groups with high prevalence of HCV, including dialysis patients, people who have been incarcerated, HIV-infected individuals, men who have sex with men (MSM) and those born in the United States between 1945-1965 (“baby-boomers”).

Additionally, screening is recommended for patients with high risk of virus transmission, such as pregnant women.

Worldwide, some programs have focused efforts for HCV screening on patients arriving at the emergency department (ED). The reasoning behind this strategy is mainly the over-representation of at-risk groups in this population, including PWID, immigrants, etc.[3,4]. Studies have shown a higher prevalence of HCV among ED patients compared to the general population[5-8]. Furthermore, HCV-infected patients utilize more medical services than non-HCV carriers[9], and have more ED visits[10,11]. The ED often serves as a “safety net” for these vulnerable populations, providing unique access to them[9].

In a single-center United States based study from 1992, 18% of all patients presenting to an inner-city hospital ED were positive for HCV[12]. A study by Hsieh et al[13] from an american urban ED screened all patients arriving at the ED during an 8-wk period. 13.8% of patients had positive anti-HCV antibodies, with 31.3% of them previously undiagnosed. The study estimated that 25% of newly diagnosed patients would not have been screened using risk-/birth-cohort based testing, and suggested a practice of 1-time universal testing for all ED attendees.

A Swiss study from 2007 screened 5000 patients arriving to the ED for various complaints, with an anti-HCV prevalence twice as high as the general population[14]. Finally, a study conducted in tertiary care EDs from Germany screened 28809 patients unselectively for anti-HCV antibodies, with an overall prevalence of positive screening of 2.6%, compared to an estimated 0.4%-0.6% in the German population, and overall positive HCV- polymerase chain reaction (PCR) in 1.6%[15]. Nineteen percent of HCV-RNA positive patients were previously undiagnosed.

All these studies were conducted in the pre-direct acting anti-viral agents (DAA) era and did not assess linkage to care. One study conducted in an urban ED in the United States at 2013 screened “baby boomers” arriving in the ED. Of 102 patients diagnosed with HCV, only 20% attended an initial appointment with a liver specialist[16].

Recently, a study conducted in an ED in Melbourne, Australia was published[17]. In this study, comers to the ED were screened for risk factors and were offered the OraQuick® oral HCV antibody test. Those with positive results had confirmatory testing with HCV-RNA, 34% of participants screened reported at least one risk factor. Of those, 14% had a reactive result on OraQuick®. Among the patients with positive HCV-RNA, 37% commenced treatment and 70% of these obtained a cure.

Data regarding the epidemiology of HCV in Israel is limited. A systematic review by Cornberg et al[18] estimated HCV prevalence in Israel at 1.96% of the population, while prevalence among immigrants from the former Union of Soviet Socialist Republics (USSR) was 4%. It was estimated that approximately 27000, or 33% of infected patients were already diagnosed. Risk factors for HCV carrier state in Israel include: immigration from the former USSR; PWID, current or past; reception of blood transfusions before 1992; close contact with infected individuals; and surgery.

In this study, we implemented a screening program in high risk populations attending our ED in order to assess the prevalence of undiagnosed HCV in this population and to analyze linkage to care.

**MATERIALS AND METHODS**

**Patient selection**

This was a single-center prospective trial. Patients arriving at the ED in Tel-Aviv Medical Center for any cause and their accompanying parties in selected days during March-August 2018 were screened via questionnaire for risk factors for HCV infection. Inclusion criteria were: Ages 18-75, ability to give consent, clinical stability and at least one positive answer for risk factors on the verbal questionnaire. Exclusion criteria were a known HCV diagnosis (as reported on initial screening) and special populations (pregnant women, children). Patients declaring a known HCV diagnosis were immediately offered a referral to the hepatology clinic for further treatment.

The questionnaires were administered by clinicians from our research team who worked in shifts in the ED, additional to ED personnel. Shifts varied in hours during the day, not including night shifts. Non-critical patients and their accompanying
parties were approached, and those consenting to participate were screened. Initially, verbal screening was conducted to identify those with risk factors. The verbal questions included country of birth, a known HCV diagnosis, and the different risk factors as in the written questionnaire. Those with at least one positive answer were given a written questionnaire.

The written questionnaire included 9 questions for established national and international risk factors for HCV infection. The risk factors screened for were: Exposure to blood transfusion, blood products or organ transplantation before 1992; those born in countries from the former USSR; current/past IV drug use; HIV carriers; MSM; those born to HCV-infected mothers; prior prison time; and chronic kidney disease (CKD). Additionally, participants were asked of prior knowledge of a diagnosis of HCV.

Those with any positive answer for a risk factor on the questionnaire were tested for HCV.

The study was conducted in compliance with the declaration of Helsinki and was approved by the Institutional review board (IRB) (0634-16). All participants screened gave informed consent.

**HCV Testing**

Two screening methods were used. All participants were planned for OraQuick® testing (based on availability of the kit), that detects HCV antibodies in saliva[26]. The OraQuick® is a highly accurate, rapid, point-of-care test for HCV antibodies, with sensitivity of 98.1% in oral fluid and specificity of 100%[27].

Participants who had blood taken in the ED for other reasons also had serology testing for anti-HCV antibodies.

Patients who tested positive for HCV on either screening test were referred to complete HCV-RNA-PCR and HCV genotype testing via healthcare providers.

**Patient contacts**

Multiple attempts at contacting patients testing positive for HCV were made via phone calls to numbers given by the patients at the time of signing informed consent and those in electronic medical records. Contact was also attempted though opioid substitution therapy clinics for 3 patients, and through HIV clinics for 2 patients.

**Statistical analysis**

Descriptive analyses were performed for all variables. Continuous data are reported as mean ± SD, and categorical data are presented as percentages. Univariate analyses were used for the comparison of variable's distribution between the study groups. To test differences in continuous variables between two groups the independent samples \( t \)-test was used. To test the differences in categorical variables the Pearson Chi-Square test was performed, \( P < 0.05 \) was considered statistically significant for all analyses. We used stepwise Logistic Regression analysis for prediction modeling of positive HCV testing according to the risk factors. All statistical analysis was performed using SPSS version 25.0 for Windows (SPSS Inc., Chicago, IL, United States). The statistical methods of this study were reviewed by Dr. Liat Deutsch from Tel-Aviv medical center.

**RESULTS**

**Study population**

Five hundred and forty-one participants had at least one positive answer and formed the study group. Fifty three percent of participants were male. The average age was 47.2 ± 15.3 years (range 19-88). Seventy one percent of participants were patients arriving for care in the ED, while 29% were their accompanying party.

As shown in Figure 1A, most participants had only one risk factor for HCV infection. Figure 1B details the risk factors among the participants. The most common risk factor was immigration from the former USSR (76% of participants).

**Positive HCV screening**

All participants had at least one HCV diagnostic test performed. All were planned for OraQuick® testing, though only 88% (476/541) underwent the test due to kit availability. Thirty six percent (199/541) of all participants who had blood drawn in the ED for other reasons had serology testing. Twenty five percent (134/541
Seventeen participants (3.1% of all screened, CI: 1.8%-5%) were positive for HCV (Table 1). Two participants who had a negative OraQuick® but positive serum anti-HCV had lower antibody levels than other positive participants. One of the two later completed testing for HCV-RNA-PCR which was negative, coinciding with previous reports indicating the sensitivity of the test from oral fluids is lower in non-viremic patients\cite{27,28}. Twelve of the HCV-positive patients had a previous diagnosis of HCV infection. Five of them answered negatively in the initial screening to the question of a known HCV diagnosis, but later reported a known HCV diagnosis in the written questionnaire. In examining prior medical records, we found 7 additional patients who had a previous diagnosis of HCV but were unaware of it. They all had not received anti-viral treatment and were not followed up by a hepatologist.

Table 2 compares the characteristics of the anti-HCV positive to negative groups. Most of the patients testing positive for HCV had multiple risk factors (Figure 2A), the most common being IV drug use (82%) and serving time in prison (65%) (Figure 2B). Univariate analysis showed that gender, PWID, HIV carriers, and time served in prison were all associated with positive HCV screening. Patients positive for HCV were less likely to have been born in the former USSR, though this is most probably a selection bias, as the participants were screened based on known risk factors. The only risk factor that remained independently associated with positive HCV screening in the multivariate analysis was PWID ($P < 0.001$, Table 3).

Our cohort did not show increased risk for HCV in CKD patients or those who had received blood products/organ transplant prior to 1992, though this may be due to the...
### Table 1 Screening results of hepatitis C virus-positive patients

| Patient ID | OraQuick® | anti-HCV | Anti-HCV levels |
|------------|-----------|----------|-----------------|
| 84         | Positive  | Positive | 11 <            |
| 195        | Positive  |          |                 |
| 263        | Positive  | Positive | 11 <            |
| 267        | Positive  | Positive | 11 <            |
| 333        | Positive  |          |                 |
| 348        | Positive  | Positive | 11 <            |
| 373        | Positive  | Positive | 11 <            |
| 374        | Positive  | Positive | 11 <            |
| 410        | Positive  | Positive | 11 <            |
| 413        | Negative  | Positive | 1.35            |
| 422        | Negative  | Positive | 9.67            |
| 424        | Positive  | Positive | 11 <            |
| 426        | Positive  |          |                 |
| 428        | Positive  | Positive | 11 <            |
| 435        | Positive  |          |                 |
| 490        | Positive  |          |                 |
| 515        | Positive  |          |                 |

Seventeen patients screened positively on either OraQuick® or serum anti-hepatitis C virus antibodies. HCV: Hepatitis C virus.

### Table 2 Patient characteristics

|                     | HCV negative (% of patients, n = 524) | HCV positive (% of patients, n = 17) | P value |
|---------------------|---------------------------------------|-------------------------------------|---------|
| Males               | 52                                    | 93.8                                | 0.001   |
| Born in the former USSR | 77.9                                | 47.1                                | 0.003   |
| PWID                | 1.1                                   | 82.4                                | < 0.001 |
| Served time in prison | 8.6                                   | 64.7                                | < 0.001 |
| HIV                 | 1.7                                   | 23.5                                | < 0.001 |
| MSM                 | 8.4                                   | 0.0                                 | 0.212   |
| Received blood products prior to 1992 | 8.4                                  | 0.0                                 | 0.213   |
| Mother with HCV infection | 2.1                                  | 0.0                                 | 0.546   |
| Received organ transplant prior to 1992 | 0.2                                  | 0.0                                 | 0.857   |
| Chronic kidney disease | 7.1                                  | 5.9                                 | 0.85    |

HCV: Hepatitis C virus; USSR: Union of Soviet Socialist Republics; PWID: People who inject drugs; HIV: Human immunodeficiency virus; MSM: Men who have sex with men.

small sample size. Interestingly, although the study included 8.5% MSMs, none were found to be HCV positive, suggesting that this risk factor might be less significant than previously assumed.

Among all self-reported PWID’s in the cohort, anti-HCV prevalence was 70% (14/20), while among participants who served time in prison the prevalence was 19.6% (11/56). These data concur with previous publications where among PWID, HCV prevalence ranged from 35%[29] to 75%[30].
### Table 3 Multivariate analysis of risk factors for hepatitis C virus

| Variable                                | Univariate logistic regression | Multivariate logistic regression |
|-----------------------------------------|--------------------------------|---------------------------------|
|                                         | Exp (b)           | 95%CI | P value | Exp (b) | 95%CI | P value |
| Gender (female vs male)                 | 0.072             | 0.009-0.55 | 0.011   | 0.578   | 0.043-7.71 | 0.679  |
| PWID (yes vs no)                        | 402.889           | 91.3-1777.1 | < 0.001 | 188.95  | 33.88-1053.82 | < 0.001 |
| Served time in prison (yes vs no)       | 19.515            | 6.89-55.25 | < 0.001 | 4.076   | 0.623-26.67 | 0.143  |
| HIV (yes vs no)                         | 17.6              | 4.8-64.6  | < 0.001 | 5.32    | 0.242-116.78 | 0.289  |
| Born in the former USSR (yes vs no)     | 0.25              | 0.09-0.67 | 0.006   | 0.562   | 0.092-3.42 | 0.532  |

Dependent variable: Hepatitis C virus positive. PWID: People who inject drugs; HIV: Human immunodeficiency virus; USSR: Union of Soviet Socialist Republics.

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**Figure 2** Number of risk factors per hepatitis C virus-positive patient and distribution of risk factors. A: Risk factors per patient. 76.5% of participants with positive hepatitis C virus (HCV) screening had more than one risk factor per patient; B: Distribution of risk factors among HCV-positive patients. The most common risk factors among HCV-positive patients were IV drug use and prior prison time. HCV: Hepatitis C virus; USSR: Union of Soviet Socialist Republics; MSM: Men who have sex with men; HIV: Human immunodeficiency virus; CKD: Chronic kidney disease.

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**Linkage to care**

Multiple attempts were made to contact patients with positive HCV results. Of the 17 patients found positive in this study, none received anti-viral treatment at the end of follow-up. Two of the patients died from non-liver related diseases. One patient
completed a blood test for HCV-RNA-PCR that was negative. Three patients were interested in treatment in initial phone conversations; however, they did not arrive for clinic appointments. Eleven of the patients, mostly PWID or homeless, had no updated contact information and were unreachable.

DISCUSSION

High-risk targeted HCV screening in the ED identified higher rates of HCV, compared to previously published HCV prevalence rates in the Israeli general population (3.1% compared to 1.96% [25]). More than half of the HCV-positive patients identified in our study had a previous diagnosis, but most were unaware of the diagnosis and none were treated or followed-up in a hepatology clinic.

Linkage to care in this population proved difficult, and despite repeated efforts, none have started anti-viral treatment during 1 year of follow up. Many of the HCV-positive patients were homeless and without correct contact information. Since the results of the screening tests were available usually 24 h after the ED visit, patients had already been discharged by that time. Similar issues were described in studies in other countries [30,31]. One study in an American urban hospital targeted PWID’s for screening at ED visits. Although HCV prevalence was 26% in the individuals tested, only 1/22 was treated at 1 year follow-up [32].

Additionally, all Israeli citizens have medical insurance and access to medical care, thus the ED serves as a “safety net” for extreme cases only. These findings suggest that though ED screening in Israel may identify HCV infection in high-risk patients, some of whom are otherwise without regular medical care, this does not improve treatment rates.

Screening with OraQuick® had similar results to anti-HCV serum antibodies. Our study design did not allow to accurately assess the performance of the test, though previous publications and the high correlation with serum antibody levels suggests that this is a good alternative for HCV blood testing and may allow quicker response times and better access to difficult-to-screen populations.

The extremely high prevalence of HCV infection among PWID and people who were incarcerated suggests that these populations are an essential and critical target for intervention in order to achieve viral elimination, as shown also in the Australian study [24].

Future avenues for investigation include targeted screening in high-risk populations, conducted in facilities with long-term follow-up to ensure linkage to care, such as opioid substitution therapy clinics, HIV clinics, prisons etc. Additionally, further studies will be needed to address whole-population non-targeted screening in order to assess linkage to care in these populations. Furthermore, efforts are being made to identify previously diagnosed but yet untreated patients and link them to care.

Our study had several limitations. This was a single-center study in an urban city hospital that has a relatively large population of high-risk patients. Thus, the relatively high prevalence of HCV may not be indicative of other EDs in Israel. Additionally, risk factors were patient-reported and thus are prone to biases related to this method. Only patients who were clinically stable and able to give informed consent were included, thus excluding high-risk groups, such as intoxicated patients, those with mental health issues, etc. Finally, the number of HCV-positive patients was low.

In conclusion, although we identified more HCV carriers than the expected population rate, ED targeted-screening of high-risk patients did not improve anti-viral treatment rates.
population. Prior studies showed that HCV prevalence in emergency department attendees is higher than the general population.

**Research objectives**

A single center prospective study, aimed at identifying undiagnosed HCV carriers among high risk emergency room attendees and linking them to anti-viral treatment.

**Research methods**

Persons visiting the emergency department were screened by a 9-question risk factor-specific questionnaire. Those with at least one risk factor were tested for HCV with blood and saliva antibody tests.

**Research results**

Five hundred and forty-one participants were tested for HCV. Eighty five percent of participants underwent saliva testing, 34% were tested for serum antibodies, and 25% had both tests. 17 patients (3.1%) had a positive result, compared to local population incidence of 1.96%. Eighty two percent of patients who inject drugs, and 64% served time in prison. Twelve patients were found to have been previously diagnosed with HCV but were unaware of the diagnosis. At 1-year follow-up, only one patient completed HCV-RNA testing and was found negative. None of the remaining patients completed the recommended testing, visited a hepatology clinic or received anti-viral treatment.

**Research conclusions**

Targeted high-risk screening in the emergency department identified undiagnosed and untreated HCV carriers, but did not improve treatment rates.

**Research perspectives**

This study suggests that in order to achieve viral elimination, other avenues need to be explored to find a framework that will enable treatment completion for this population.

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