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Point-of-care Hepatitis C virus testing and linkage to treatment in an Australian inner-city emergency department

J. Hutton[a,b,*], J. Doyle[c,d,e], R. Zordan[b,f], T. Weiland[b,f], A. Cocco[a,b,f], J. Howell[c,d], S. Iser[a,b], J. Snell[c,f], S. Fry[c], K. New[c], R. Sloane[c], M. Jarman[c,f], D. Phan[c,f], S. Tran[c,f], A. Pedrana[d], B. Williams[d], J. Johnson[g], S. Glasgow[c], A. Thompson[c,f]

[a] Emergency Department, St Vincent's Hospital Melbourne, Australia
[b] Emergency Practice Innovation Centre, St Vincent's Hospital Melbourne, Australia
[c] Gastroenterology Department, St Vincent's Hospital Melbourne, Australia
[d] Burnet Institute, Melbourne, Australia
[e] The Alfred and Monash University Department of Infectious Diseases, Melbourne, Australia
[f] University of Melbourne, Melbourne, Australia
[g] Australian Research Centre in Sex, Health and Society, La Trobe University, Melbourne, Australia

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ABSTRACT

Background: In Australia, Hepatitis C Virus (HCV) treatment is declining, despite broad access to direct-acting antiviral medication. People who inject drugs are proportionally over-represented in emergency department presentations. Emergency department assessment of people who have injected drugs for HCV presents an opportunity to engage this marginalised population with treatment. We describe the outcomes of risk-based screening and point-of-care anti-HCV testing for emergency department patients, and linkage to outpatient antiviral treatment.

Methods: During the three-month study period, consecutive adult patients who presented to the emergency department during the study times were screened for risk factors and offered the OraQuick oral HCV antibody test. Those with reactive results were offered venepuncture in the emergency department for confirmatory testing and direct-acting antiviral treatment in clinic. The main outcome measures were the number and proportion of viremic participants that were linked to the hepatitis clinic, commenced treatment and achieved a sustained viral response. Secondary outcome measures were the proportion (%) of presentations screened that were oral antibody reactive, and the prevalence and type of HCV risk factors.

Results: During the study period, 2408 of the 3931 (61%) presentations to the emergency department were eligible for screening. Of these 2408 patients, 1122 (47%) participated, 307 (13%) declined participation and 977 (41%) could not be approached during their time in the emergency department. Among the 1122 participants, 378 (34%) reported at least one risk factor. Subsequently, 368 (97%) of the 378 participants underwent OraQuick anti-HCV test, and 50 (14%) had a reactive result. A risk factor of ever having injected drugs was present in 44 (88%) of participants who were sero-positive. Of the 45 that had blood tested, 30 (67%) were HCV ribonucleic acid (RNA) positive. Three participants died. Of the 27 remaining participants, 10 (37%) commenced treatment and 7 of these 10 (70%) obtained a cure. There was a high rate of homelessness (24%) among anti-HCV positive participants.

Conclusion: Among emergency department participants with a risk factor for HCV, positive serology was common using a rapid point-of-care test. A history of injecting drug use was identified as the risk factor with highest yield for positive HCV serology, and is suitable as a single screening question. However, linkage to care post ED presentation was low in this marginalised population. There is a need for new pathways to improve the care cascade for marginalised individuals living with HCV infection.

* Corresponding author at: Emergency Department, St Vincent's Hospital Melbourne, 41 Victoria Parade, Fitzroy, VIC, 3065, Melbourne, Australia.
E-mail address: jennie.hutton@svha.org.au (J. Hutton).

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Introduction

Direct-acting antivirals now offer curative treatment and prevent long-term consequences of chronic HCV infection such as cirrhosis and hepatocellular carcinoma (Carrat et al., 2019). All Australians are eligible for treatment with direct acting anti-virals. Whilst rates of treatment uptake were very high in the first year this treatment became available, rates have been declining since (Doyle et al., 2019; Hajarizadeh, Grebely, Matthews, Martinello, & Dore, 2018). As Australia aims for elimination of HCV as a public health threat by 2030, the major challenge is to engage marginalised individuals in care. Without efforts to improve testing and linkage to care, treatment access alone may not be sufficient to achieve HCV elimination targets (Scott, Doyle et al., 2017). Recent modelling has concluded that reduced incidence rates and mortality targets could be achieved if treatments are targeted at people who inject drugs (PWID), the most common risk factor for HCV transmission in Australia (Scott, McBryde, Thompson, Doyle, & Hellard, 2017). An annual treatment rate of 8% of all people who have a history of injecting drug use would eliminate HCV in Australia in ten years (Martin et al., 2013).

People who inject drugs present to emergency departments at a rate at least three times higher than the general population (Nambiar, Spelman, Stoove, & Dietze, 2018), and for reasons most often not related to overdose. The prevalence of HCV has been established in emergency department settings internationally, and ranges from 1 to 14% (Allison et al., 2016; Anderson et al., 2016, 2017; Lyons et al., 2016; O'Connell et al., 2016; Orkin et al., 2016; White, Anderson, Pfeil, Trivedi, & Alter, 2016; Wong et al., 2019). There are no Australian studies that have explored the prevalence of HCV risk factors in patients presenting to the emergency department. The International Viral Hepatitis Elimination Meeting in 2018 identified the need to gather insights regarding successful approaches for HCV identification and treatment in different populations, as diagnostic tests become more affordable and direct-acting antiviral treatment are more available (Popping et al., 2018).

The aim of this study was to evaluate the feasibility of screening for HCV infection in people presenting to the emergency department using the combination of risk factor questionnaire and rapid point of care HCV antibody testing. We also evaluated cascade of care from HCV diagnosis the emergency department through to cure, as defined as a sustained viral response (SVR) twelve weeks after completion of treatment.

Methods

Study design

This study was a prospective interventional study to evaluate the feasibility of screening for HCV infection for HCV infection in people presenting to the emergency department using a combination of risk-based screening and rapid point-of-care antibody testing.

Setting

The study was performed in an emergency department is located at an inner-city tertiary referral hospital in Melbourne with ˜46,000 adult attendances annually. Participants were recruited between 1st June to 31st August 2017. Treatment and follow-up occurred from June 2017 to August 2018.

Participants

Patients were eligible to participate if they presented to the emergency department within the recruitment times during the 3-month period and were over 18 years of age. Patients were excluded if they were unable to provide informed consent for any reason, such as psychiatric impairment, intoxication, critical illness or incarceration. Patients were excluded if they left before completing the screening process, or if they had been previously screened. Pregnant woman were excluded as HCV treatment is not currently recommended in this group, and the primary objective was linkage to treatment. Patients with a known diagnosis of HCV were not excluded. If the patient's primary language was not English, interpreters were used. Using a consecutive sampling method, emergency department-based screening and testing occurred on weekdays by research staff covering the 12-h period, 9am–9pm. Six-hour shifts (n = 10) were completed on weekends and overnight to include a representative sample of patients. Emergency research staff completed a four-hour training session provided by employees from the Australian Research Centre for Sexual Health and Society. This included training in pre- and post-test discussion. Training in the administration and interpretation of the OraQuick (Orasure Technologies, Pennsylvania, U.S.A.) oral point-of-care anti-HCV test was conducted by a company representative.

Research staff screened triage notes to ascertain patient eligibility, and, where required, treating staff were approached to confirm eligibility. Patients who agreed were provided with a patient information and consent form. Once informed consent was gained, participants were verbally administered a brief screening tool consisting of questions relating to any prior diagnosis and treatment of HCV, and risk factors associated with HCV. Declining patients were asked what their HCV status was, if known. This information was voluntary. The OraQuick (Orasure Technologies, Pennsylvania, USA) oral point-of-care anti-HCV test was offered to all consenting participants who screened positive for at least one risk factor. If the point-of-care anti-HCV test was reactive, confirmation serology testing for HCV antibody (Architect, Abbott Diagnostics, Illinois, USA) and ribonucleic acid (RNA) (COBAS 4800 HCV Assay and COBAS HCV GT Assay, Roche, Sydney, Australia) to detect chronic active infection and genotype was requested from blood samples taken in the emergency department.

Participants who underwent confirmatory blood testing were given results by telephone, counselled, and provided with an outpatient clinic appointment. A reminder telephone call was made prior to the appointment, and a letter sent to the participants. At least three attempts were made to contact the participant by telephone to arrange an outpatient appointment. If the participant had no telephone number, alternative means of contact provided by the participant were used such as liaison with key-workers. Direct-acting antiviral treatment was prescribed as appropriate for HCV genotype, and clinical considerations. Participants who did not attend the outpatient clinic appointment received a phone call from the clinic nurse, their general practitioner was notified, and an appointment was re-booked. This process was repeated three times prior to the participant being considered lost to follow-up. Participants were considered cured if they obtained a Sustained Viral Response. A Sustained Viral Response (SVR) was defined as having undetectable HCV RNA 12 weeks after completion of treatment.

Variables

Demographic and follow-up data

Routinely collected clinical and demographic data were retrieved from the hospital electronic health records retrospectively to inform the study. The continuum of care included the number and percentage that: (1) screened positive for risk factors; (2) were HCV antibody positive; (3) were referred to clinic; (4) had bloods taken in the emergency department; and (5) were HCV RNA PCR positive. Subsequent to leaving the emergency department, this included the number and percentage of tested participants that: (6) commenced treatment following consultation; (7) completed treatment (defined as verbally reported completion of treatment); and (8) obtained treatment success by having obtained a Sustained Viral Response.

HCV risk factor screening questionnaire

The screening questionnaire was developed by the authors, including expert hepatologists, and was based on Australian guidelines (Australia, 2016). This questionnaire requested information on the participants: current or past injecting, previous incarceration, HIV infection, receiving blood products prior to 1990, having a tattoo or piercing in an unregulated environment, a needle-stick injury or a mother with HCV. Birth, residence or medical procedures in high risk countries were included as risk-factors. Countries were considered at a high risk of HCV if the country prevalence was > 6%, and areas were considered at high risk if rate was > 3% (Petruzziello, Marigliano, Loquercio, Cozzolino, & Cacciapuoti, 2016) (Supplementary Information 2). Having had a risky household contact such as sharing razors was originally included, however, is not recommended in current guidelines.

Point-of-care oral anti-HCV test

The OraQuick® Oral Fluid anti-HCV test (Orasure Technologies, Pennsylvania, USA) has > 98% accuracy with sensitivity 95.9% – specificity 99.4% (Khuroo, Khuroo, & Khuroo, 2015; Tang et al., 2017). The mouth swab was administered by research staff, who had all completed training. Results were obtained at 20 min (Smith et al., 2011) (Supplementary Information 3).

HCV serology testing

Hepatitis C antibody testing was performed by Chemiluminescent microparticle immunoassay (Architect, Abbott Diagnostics, Illinois, USA), with confirmation of positive results with the Liason XL MUREX HCV Assay. HCV polymerase chain reaction ribonucleic acid and viral load was undertaken with COBAS 4800 HCV Assay (Roche, Sydney, Australia) and the COBAS HCV GT Assay (Roche, Sydney, Australia) was used to ascertain the HCV genotype.

Potential bias

It has previously been identified that under-reporting of risk-factors such as intravenous drug use occurs in the emergency department (Lyons et al., 2016). In an attempt to reduce this bias, the research staff were provided with focused training, a private environment was provided, and the study was designed such that the screeners were independent of the patient's treating team. Consideration was also given to the fact that participants were being offered curative treatment.

Outcome measures

The primary outcome was the number and percentage of eligible patients who completed each stage of the HCV continuum of care. The secondary outcome was the number and proportion of participants that, having reported a risk factor, were oral anti − HCV positive.

Study size

To investigate the feasibility of this linkage-to-care pathway, we estimated the minimum numbers required at enrolment that would lead to at least fifteen patients requiring treatment for HCV. Previous estimates of anti-HCV prevalence in emergency departments in countries other than Australia have been between 2% and 14% (Anderson et al., 2016; Lyons et al., 2016; Orkin et al., 2016; White, Anderson, Pfeil, Trivedi et al., 2016; Wong et al., 2019). Subsequently, we calculated that 1100 participants would be expected to result in at least twenty-two anti-HCV positive participants, of which approximately seventeen would require treatment. Participation rates from similar studies in emergency department have been estimated to be a minimum of ˜28% (Allison et al., 2016; Lyons et al., 2016; White, Anderson, Pfeil, Trivedi et al., 2016). We determined that we required a minimum of ˜3900 patients to enrol ˜1100 participants. We estimated that a study period of at least 90 days would be required to achieve this figure during the study hours.

Statistical analysis

Prevalence data were reported descriptively using number and percentage (95% CI). Pearson's Chi Square and Fisher's Exact test were used to test association between categorical variables as appropriate. Multivariate analysis was conducted using a forward stepwise procedure including those variables reaching 0.2 level of significance in univariate analysis. Two-tailed tests of significance at $p < 0.05$ were used in all inferential tests. All analyses were conducted using SPSS v24.

Ethics approval

Ethics approval was sought and obtained from the St Vincent's Hospital Melbourne Human Research Ethics Committee (HREC/16SVHM/60).

Results

There were 3931 presentations for the 92-day period during recruitment times. Of these, 2408 (61%) were eligible. There were 1431 (59%) participants included in the study, and 977 (41%) were not approached due to time limitations. There were 1124 (79%) individual participants approached who consented to participate, and 307 (21%) declined. A reason was given for non-participation in 40 (13%) of patients, as outlined in Fig. 1.

The characteristics of the 1122 participants that were enrolled in the study are detailed in Table 1. The participants enrolled had similar characteristics to adult emergency department patients at the hospital in 2017, whereby 54% were male, the median age group was 40–49 years, and 2.3% were Aboriginal.

The overall prevalence of anti-HCV positive participants in the emergency department as identified by initial risk factor screening, was 4.5% (50/1122). Of the 50 anti-HCV patients identified, 8 (16%) were newly diagnosed as self-reported by participants. The characteristics of POC anti-HCV positive and negative participants are shown in Table 2. A reactive anti-HCV test was more common in those at-risk participants who were born in Australia, Aboriginal, homeless or pension recipients (Table 2).

The number and proportion of risk factors associated with a reactive anti-HCV test are shown in Table 3. Of those that had a reactive anti-HCV test, 44 (88%) reported ever having injected drugs. Univariate analysis showed that risk factors associated with being HCV antibody positive were; a history of injecting drugs, incarceration, having had a tattoo or piercing in an unregulated environment, living with an anti-HCV positive person or having had a positive HIV test. The final model did not include living in a household with an HCV positive person as this is not included in the risk factor guidelines and it had high multicollinearity (VIF > 3). There were no participants that reported this as their only risk factor. A history of injecting drug use was associated with a greater odds of being anti-HCV positive [adjusted odds ratio of 34.22 (95% CI 13.21–88.69)]. The model developed by applying binary logistic regression analysis correctly predicted 96% of cases where the oral test was negative, and 66% of cases where the oral test result was positive, giving an overall percentage correct prediction rate of 92%.

The numbers and percentages of participants that progressed through the stages in the continuum of care are illustrated in Fig. 2. In brief, 67% (30/45) were HCV RNA positive. Three anti-HCV positive participants died during the follow-up period, two from unrelated malignancies, and one from liver failure. Among people who were HCV RNA positive, clinical review occurred in 37% (10/27) and all of these commenced treatment. 63% (17/27) were lost to follow-up. A sustained viral response was documented in 70% (7/10). The median time from emergency department presentation to commencement of treatment was 56 days (IQR 21-118). The three patients who did not achieve a cure had treatment started via an outreach program rather than clinic, reported being homeless and adherence to medication was suboptimal. No adverse events occurred during the course of the study.

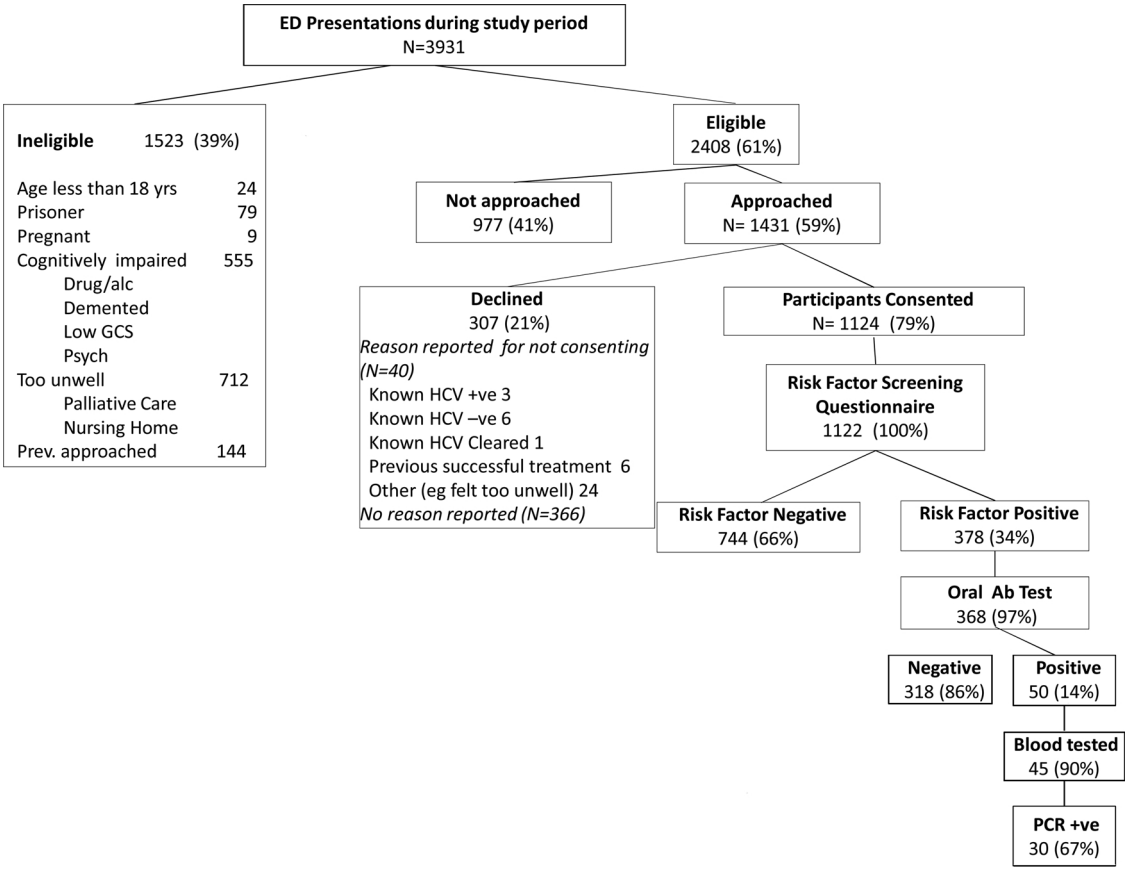

Fig. 1. Study flow diagram.

Table 1
Characteristics of screened participants (n = 1122).

	Screening Performed		95% CI
Mean age years (SD)	49	4.1	
	N	%	
Male	610	55	52.29 – 58.11
Female	512	45	41.89 – 47.71
Born in Australia	730	66	63.64 – 69.16
Preferred Language English	1058	96	94.85 – 97.15
Aboriginal	22	2	1.18 – 2.82
Homeless (At hospital registration)	22	2	1.18 – 2.82
Pension recipient	413	36	33.19 – 38.81
Deceased at 12-week follow-up	17	2	1.18 – 2.82
Previously tested for HCV	277	25	22.47 – 27.53
(Test Positive recall)	42	4	2.85 – 5.15

Risk factors for HCV[a]	n = 378	% of total	95% CI
Ever injected drugs	92	8	6.41 – 9.59
Tattoos /Piercings	100	9	7.33 – 10.67
History of incarceration	84	8	6.41 – 9.59
Needle-stick Injury	114	10	8.24 – 11.76
Blood product recipient pre-1990	46	4	2.85 – 5.15
Previous HIV test	15	1	0.42 – 1.58
Mother anti-HCV positive	12	1	0.42 – 1.58
Household contact anti-HCV positive	89	8	6.41 – 9.59
Born OS /High prevalence country	17	2	1.18 – 2.82
Lived OS/High prevalence country > 2 yrs	19	2	1.18 – 2.82
Lived in a refugee camp	4	< 1	0.0 – 0.9
Invasive procedure in a high prevalence country	3	< 1	0.0 – 0.9

[a] Multiple responses possible.

Discussion

We have shown that risk-factor based screening in the emergency department, paired with rapid point of care HCV serology testing is effective for identifying people living with hepatitis C. The prevalence of anti-HCV positive emergency department participants was 4.5%. The prevalence of HCV RNA positive participants was 2.7%. A single question regarding injecting drug use identified most (88%) of the anti-HCV positive participants. However, linkage to care was not successful, as only seven (26%) of the 27 patients identified with chronic infection obtained a cure.

The prevalence of 2.7% HCV positive participants identified by this method is higher than the estimated prevalence in the Australian population of 0.9% (Australia, 2016), reflecting the higher rates of ED presentations among marginalised individuals with risk factors for HCV. Similar observations have been made overseas. In an Irish study, O'Connell and colleagues observed a prevalence of anti-HCV positivity to be 5.1% among individuals presenting to the emergency department using opt-out testing (O'Connell et al., 2016). The estimated population prevalence of anti-HCV positive population in Ireland at the time was 0.5–1.2%. O'Connell et al. reported 75% of those that were anti-HCV positive had ever injected drugs, and 33% of those that were identified as being anti-HCV positive were homeless. Higher prevalence of anti-HCV positivity in ED populations has also been described in the UK and US (1.1–14%) (Allison et al., 2016; Anderson et al., 2016, 2017; Lyons et al., 2016; White, Anderson, Pfeil, Trivedi et al., 2016; Wong et al., 2019).

The rate of anti-HCV positive individuals will depend on the methodology used. Different approaches that have been used in the literature include: (a) universal screening with blood tests; (b) opt out testing; and (c) screening for HCV risk factors before testing blood.

Table 2
Characteristics of Point of Care anti-HCV positive and anti-HCV negative participants.

	Anti-HCV Positive (n = 50)		95% CI	Anti-HCV Negative (n = 318)		95% CI	P
Mean age years (SD)	45	(10.7)		47	(17.1)		
	N	%	%	n	%	%	
% Male	36	72	(58 – 84)	186	59	(53 – 64)	0.060
Born in Australia	42	84	(71 – 93)	211	67	(60 – 71)	**0.013**
Preferred Language English	48	96	(86 – 100)	309	98	(95 – 99)	0.551
Aboriginal	5	10	(3 – 22)	7	2	(1 – 5)	**0.004**
Homeless (recorded at hospital registration)	12	24	(13 – 38)	8	2.5	(1 – 5)	< **0.001**
Pension recipient	37	74	(60 – 85)	114	36	(31 – 41)	< **0.001**
Deceased at 12-week follow-up	3	6	(1 – 17)	4	1.3	(0 – 3)	**0.023**

Universal screening is the only method that can define true prevalence. However, universal screening of emergency department patients is not clinically feasible in Australia due to cost barriers. Opt-out screening is also expensive. It has been suggested that universal screening should be undertaken in emergency department settings, and is best achieved using existing infrastructure (Hagan, Wolpe, & Schinazi, 2013; O'Connell et al., 2016; Orkin et al., 2016).

In our study we wanted to evaluate the yield of a model of testing and linkage to care that minimised costs and maximised patient identification. Screening for risk factors prior to testing is a fast and cheap alternative to universal testing. For emergency department-based screening to be sustainable, it must not interfere with the core service provision of timely acute care (Moran & Talan, 2011). We observed that a single risk factor was present in ˜90% of individuals found to be seropositive. Screening for only one risk factor, injecting drug-use, could be used as a simple risk question to identify patients for HCV testing in the emergency department. Whether this could be included in an emergency department triage question as part of routine practice, or whether dedicated staff would be more suitable to supervise screening is not clear from our study. Previous work has shown that dedicated screening staff in the ED limit the time cost of screening interventions in the emergency department. (Orkin et al., 2016; White, Anderson, Pfeil, Deering et al., 2016; White, Anderson, Pfeil, Trivedi et al., 2016). One major limit of using risk-factor-based screening is under reporting (Lyons et al., 2016). O'Connell et al estimated this to be at least 14% (O'Connell et al., 2016).

The reported attendance rate at outpatient clinic in the current study (30%), despite being low, is in the range of previously reported results of 14%–35% (Allison et al., 2016; Anderson et al., 2017; Franco et al., 2016; White, Anderson, Pfeil, Trivedi et al., 2016). At a practical level, contacting the participants posed a significant challenge, as many did not have a telephone or an address.

This study supports previous findings that the homeless and marginalised cohorts have difficulty attending outpatient appointments. In addition, many are unlikely to have keyworkers to assist them with these appointments (Lambert et al., 2019). Multi-disciplinary care

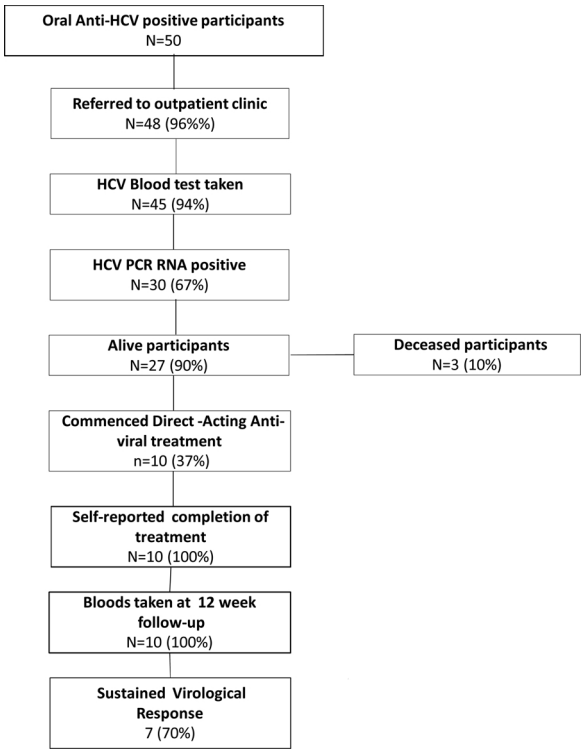

Fig. 2. Continuum of care for oral anti-HCV positive participants.

Table 3
Risk factors associated with a reactive HCV antibody test among participants who reported at least one risk factor (N = 368).

Risk Factor	Positive (N = 50) n (%)	Negative (N = 318) n (%)	Univariate Unadjusted Odds Ratio (95%CI)	p-value	Multivariate Adjusted Odds Ratio (95%CI)	p-value
Ever injected drugs	44 (88)	43 (14)	47.07 (18.92-117.11)	< **0.001**	34.22(13.21 – 88.69)	< **0.001**
History of incarceration	30 (60)	52 (16)	7.70 (4.07-14.59)	< **0.001**	4.49(1.95 – 10.31)	< **0.001**
Tattoos/Piercings (unregulated)	23 (46)	73 (23)	2.87 (1.55-5.31)	< **0.001**	2.72(1.14 – 6.48)	**0.024**
Previous positive HIV test	6 (12)	8 (3)	5.30 (1.76-15.99)	**0.003**	7.64 (1.55 – 37.69)	**0.013**
History of anti-HCV household contact	23 (46)	66 (21)	3.26 (1.76-6.06)	< **0.001**		
HCV infected Mother	2 (4)	10 (3)	1.28 (0.27-6.06)	0.749		
Needle-stick injury	14 (28)	97 (31)	0.89 (0.46 – 1.72)	0.730		
Received blood products prior to 1990	3 (6)	43 (14)	0.41 (0.12 – 1.37)	0.149		
Born overseas / high prevalence country	0 (0)	11 (4)	0.00			
Lived overseas / high prevalence country > 2yrs	0 (0)	19 (6)	0.00			
Lived in a refugee Camp	0 (0)	4 (1)	0.00			
Invasive procedure in a high prevalence country	0 (0)	3 (1)	0.00			

including support for drug dependency, social and psychological care has been shown to increase HCV testing and treatment (Bajis et al., 2017). There is a need for the development and resourcing of novel clinical pathways to engage and retain marginalised individuals in care. Case management, involvement of peer workers, and collaboration with community health-care providers, including general practitioners, harm reduction facilities and outreach nurses may be an alternative pathways to HCV treatment (Grebely et al., 2017; Scott, Doyle et al., 2017; Shand et al., 2014). In this study, we did not evaluate the feasibility of point-of-care HCV RNA testing, which might be paired with same day prescribing (test and treat from the ED). This will be an important question to address in future work. Future studies of HCV screening, identification and linkage to care from the emergency department should include health economic analysis and were beyond the scope of this study.

We acknowledge a number of limitations in the current work. However, percentage of total presentations recruited (29%) is comparable to previous opt-in HCV screening studies within emergency department settings (Allison et al., 2016; White, Anderson, Pfeil, Trivedi et al., 2016). Patients excluded for intoxication and mental health reasons may have led us to underestimate the total number of HCV seropositive individuals attending the ED. Under-reporting of risk-factors has been recognised as a limitation. Patients who are homeless are likely to represent to emergency departments and may be over-represented in the study (Moore, Gerdtz, Hepworth, & Manias, 2011). Selection bias may also have occurred if research staff selectively approached those patients that had HCV risk factors identified at triage. Since 10 of 27 participants who were positive on HCV ribonucleic acid testing were treated, our estimate for the proportion of people achieving a cure had a margin of error of 12.18%, indicating that the study was slightly underpowered to reliably assess this outcome within the usual limits of error tolerance. Finally, this study is a single-centre study in an inner-city tertiary hospital, and therefore is likely to have a high proportion of injecting drug users, and the results may not be generalisable to other emergency departments.

Conclusion

This study found that it was feasible to test a large number of people in emergency department for HCV using a risk-factor based tool and then an oral point-of-care anti-HCV test. This method identified that 4.5% of participants were anti-HCV positive, and 88% of these were identified by reporting a history of injecting drug use. However, only a small proportion (26%) participants eligible for direct-acting antiviral treatment for HCV were linked to care and achieved a cure. Many of these participants were homeless and linkage to outpatient care was a challenge. Before referral from the emergency department can be recommended as a pathway for HCV treatment, there is a need to develop models of care based in the community that support marginalised individuals.

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CRediT authorship contribution statement

J. Hutton: Conceptualization, Methodology, Resources, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition. **J. Doyle:** Conceptualization, Methodology, Resources, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition. **R. Zordan:** Conceptualization, Methodology, Resources, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition, Formal analysis. **T. Weiland:** Conceptualization, Methodology, Resources, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition, Formal analysis. **A. Cocco:** Conceptualization, Methodology, Resources, Writing - review & editing, Visualization, Project administration. **J. Howell:** Conceptualization, Methodology, Resources, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition. **S. Iser:** Methodology, Investigation, Resources, Project administration, Data curation, Supervision. **J. Snell:** Investigation, Data curation. **S. Fry:** Investigation, Data curation, Funding acquisition. **K. New:** Investigation, Data curation. **R. Sloane:** Investigation, Data curation. **M. Jarman:** Investigation, Data curation. **D. Phan:** Investigation, Data curation. **S. Tran:** Investigation, Data curation. **A. Pedrana:** Conceptualization, Methodology, Resources, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition, Formal analysis. **B. Williams:** Conceptualization, Methodology, Resources, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition, Formal analysis. **J. Johnson:** Methodology, Investigation. **S. Glasgow:** Investigation, Data curation. **A. Thompson:** Conceptualization, Methodology, Resources, Writing - review & editing, Visualization, Project administration, Funding acquisition, Supervision.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugpo.2019.06.021.

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