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Research Paper

Eradicating hepatitis C: Are novel screening strategies for people who inject drugs cost-effective?

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ABSTRACT

Background: In developed countries, people who inject drugs (PWID) have a high prevalence of hepatitis C virus (HCV), yet they are often under-diagnosed. The World Health Organization has set 2030 as a target year for HCV elimination. To meet this target, improving screening in convenient community settings in order to reach infected undiagnosed individuals is a priority. This study assesses the cost-effectiveness of alternative novel strategies for diagnosing HCV infection in PWID. Methods: A cost-effectiveness analysis was undertaken to compare HCV screening at needle exchange centres, substance misuse services and at community pharmacies, with the standard practice of detection during general practitioners' consultations. A decision tree model was developed to assess the incremental cost per positive diagnosis, and a Markov model explored the net monetary benefit (NMB) and the cost per Quality Adjusted Life Years (QALYs) gained over a lifetime horizon. Results: Needle exchange services provided a 7.45-fold increase in detecting positive individuals and an incremental cost of £12,336 per QALY gained against current practice (NMB £163,827), making this the most cost-effective strategy over a lifetime horizon. Screening at substance misuse services and pharmacies was cost-effective only at a £30,000/QALY threshold. With a 24% discount to HCV treatment list prices, all three screening strategies become cost-effective at £20,000/QALY. Conclusions: Targeting PWID populations with screening at needle exchange services is a highly cost-effective strategy for reaching undiagnosed HCV patients. When applying realistic discounts to list prices of drug treatments, all three strategies were highly cost-effective from a UK NHS perspective. All of these strategies have the potential to make a cost-effective contribution to the eradication of HCV by 2030.

Introduction

Hepatitis C virus (HCV) is a blood-borne virus that, if not treated, can cause serious and potentially life-threatening damage to the liver. New HCV treatments can cure over 95% patients (Asselah, Marcellin, & Schinazi, 2018), allowing cured patients to achieve a life expectancy equivalent to the general population. However, most chronic HCV infections are asymptomatic and are therefore only diagnosed in the later, most severe stages of the disease, where cure is less likely. In 2016, the World Health Organization (WHO) set 2030 as a target for HCV elimination (World Health Orrganization, 2016), followed by various countries setting even more ambitious elimination deadlines, such as

Abbreviations: people who inject drugs, (PWID); Hepatitis C virus, (hcv); Net monetary benefit, (NMB); Quality adjusted life years, (QALY); General practitioner, (GP); World health organization, (WHO); Substance misuse services, (SMS); Polymerase chain reaction, (PCR); Dried blood spot, (DBS); Stage liver fibrosis 0, (F0); Stage liver fibrosis 1, (F1); Stage liver fibrosis 2, (F2); Stage Liver Fibrosis 3, (F3); Stage Liver Fibrosis 4, (F4); Decompensated Cirrhosis, (DCC); Hepatocellular carcinoma, (HCC); Liver Transplant, (LT); Post-Liver Transplant, (LT + 1); IgG test for HCV antibodies, (IgG); Probabilistic Sensitivity Analysis, (PSA)

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2025 in England (APPG, 2018) and 2024 in Scotland (Health Protection Scotland, 2019). This has encouraged governments to make treatments more widely available, and subsequently, the number of patients receiving HCV treatment has increased worldwide (WHO, 2018). Whilst there have been vast improvements in HCV drug development, the availability of treatment alone is not enough to achieve WHO targets. Enhanced diagnosis and screening strategies are also required (Schröeder et al., 2019).

In the developed world, those most at risk of HCV infection are people who injects drugs (PWID), particularly individuals with unsafe injecting practices, such as sharing injecting equipment. In the UK 143,000 people are living with chronic HCV (Public Health England, 2019) and it is estimated that 90% of them have a history of injecting drug use (NICW, 2012). Yet, this number is considered to be only the "tip of the iceberg" as nearly half of people infected with HCV remain undiagnosed (Dillon, Barclay, Fraser, & Hayes, 2018; Public Health England, 2019). Therefore, to reach the 2030 goal, understanding how to prioritize screening within high-risk populations to reach infected undiagnosed individuals is crucial. In this regard, new models of care based on a complementary involvement of traditional and non-traditional sites of screening have been designed to increase patient engagement in HCV testing and treatment. These non traditional sites of screening include a variety of community settings and points of care. Given the relative newness of these sites of screening there is a need to understand their cost, cost-effectiveness and implications.

The aim of this study was to evaluate the cost-effectiveness of alternative screening strategies for targeting and diagnosing PWID for HCV infections using Tayside (Scotland, UK) as a case study. In recent years, Scotland, and in particular Tayside, has piloted a variety of novel screening strategies. Scotland's Hepatitis C Action Plan (Goldberg David., Innes, & Dillon, 2019; Goldberg et al., 2008), outlined strategies such as moving HCV screening closer to high-risk individuals, including PWIDs, in order to optimise diagnosis and engagement in care. This analysis assessed three alternative screening strategies for HCV detection in PWID that have been piloted in NHS Tayside, Scotland, and compares them to the current UK standard practice of detection during a General Practitioner (GP) consultation.

Methods

Screening strategies & model overview

The strategies we analysed were part of an extensive multipronged model of care for HCV detection developed in Tayside, Scotland. The key difference between the three novel strategies and the standard care was the location/point of care where the screening took place. Novel locations were: a) substance misuse services (SMS), b) needle exchange services, c) community pharmacies providing opiate substitute therapies and injecting equipment. Standard care was screening during GP appointment (see Table 1 for strategies' details). All the strategies were designed to simplify the cascade of care for patients, moving the point of care closer to high-risk individuals and streamlining the screening process, relying on needle exchange workers, nurses or pharmacists rather than doctors. In Tayside, these three novel strategies have all been implemented simultaneously and alongside the standard screening strategy, comprising a pilot of a single complex model of care. The baseline comparator was the current standard care practice in Scotland to detect HCV, which was a screening at a GP practice based on symptoms or high-risk factors. Patients in every strategy differed by (1) attrition across the HCV cascade of care in the short-term (2) demographics, and (3) treatment uptake (see Tables 2 and 3 for details). Testing comprises a HCV antibody test (either dried blood spot test or venous blood test) and a confirmatory PCR test for antibody positive individuals. The PCR is a venous blood test which is more expensive than the antibody test, but provides a confirmed diagnosis of active infection. Different tests require a different amount of time to obtain results, and consequently, this translated into different dynamics and attrition within the cascade. The number of people attending services differed across the strategies, as did the number of tests taken, positive tests results and user-engagement beyond initial testing. Inputs (prevalence, effectiveness, resource use estimates) for the model were derived from observational data from the pilot studies and published literature and were then supported by the knowledge of clinical experts. The model was parameterised to the Scottish and UK context through published life expectancy estimates, utility values, unit cost values and data on PWID-HCV prevalence in Scotland. Model design was based on clinical expert advice and previously published studies analysed in a literature review of economic evaluation of screening strategies for HCV detection (see Supporting Information for details). The needle exchange centre strategy data were obtained from the Cairn Centre Harm Reduction Service in Dundee, which serves approximately 50% of the people who inject drugs in Tayside (NHS Tayside audit data). Pharmacy data were derived from 33 pharmacies dispensing opiate substitute therapies and injecting equipment which provide HCV screening across NHS Tayside. The Dundee Integrated Substance Misuse Service provided the data for SMS service. General Practices across NHS Tayside provided data for the standard practice arm, however, data from this strategy referred to the general population and not to current PWIDs only. Since there is evidence suggesting that there is a higher propensity to screen PWIDs for HCV by GPs (Datta, Horwood, Hickman, & Sharp, 2014; McLeod et al., 2017), and also a likely difference in compliance in the cascade of care, a counterfactual strategy for current PWIDs was built. The counterfactual was based on the average of all the three observed PWID strategies and the available data for screening at GPs for the general population, this estimate was then validated or adjusted based on clinicians' opinions (Table 3). Assumptions regarding the likelihood of a PWID going to a specific testing location were based on advice from clinical experts directly involved in the PWID model of care. The economic analysis initially compares each strategy against the GP strategy (standard care) (pairwise comparison). Strategies are also analysed incrementally to provide the relative cost-effectiveness and

Table 1
HCV Screening strategies.

Screening Strategies:

General practitioner (GP): During a routine GP appointment, there is clinical suspicion that the patient may have HCV and a venous antibody test is requested. The blood sample is sent away for testing and the patient called back in a few days with the results. If positive, a PCR test is also requested. If the result is positive, this is fed back with a further contact to the patient in a few days by the requesting healthcare worker and onward referral is made to HCV specialist services.

Substance Misuse Services: Clients who are being assessed to begin receiving Opiate Substitute Therapies (OST) by the Tayside Substance Misuse Service (SMS), or who are already on an OST, are offered a hepatitis C test. A dried blood spot (DBS) test is taken by an addiction worker at the SMS. Positive antibody tests on DBS are then directly referred to a HCV specialist nurse on site taking routine blood tests and HCV PCR, or working close by in a Needle exchange centre (5 min walking time). If the person is confirmed to have HCV, the patients is contacted in few days to start the treatment, either initiated by the community pharmacists dispensing OST or the HCV specialist nurses in the outreach clinics.

Pharmacies: Clients attending participating community pharmacies to collect their OST are opportunistically offered a HCV test if not previously tested. Clients with positive DBS antibody tests receive a subsequent confirmatory HCV RNA and genotype testing, and their results are delivered in a few days. If HCV infection is confirmed, clients are referred to a HCV service and then they initiate treatment via the community pharmacist or are referred to the HCV specialist nurses for review and treatment in a HCV outreach clinic. Pharmacies running screenings receive fees per patients for using tests, administrative costs and to manage the risk of ordering high cost medications.

Needle exchange centres: People attending the needle exchanges are offered HCV testing via DBS by trained staff at the needle exchange service. If positive, patients are referred to a HCV nurse who take routine bloods tests, including HCV RNA, on site. If the HCV RNA is positive the clients are then contacted in few days and invited to attend an outreach clinic at the needle exchange centre to be started on HCV eradication.

Table 2
Cohorts' figures.

Observational data	Individuals with lgG positive[1]	HCV+ detected	No. individuals with HCV stage assessment	Average age
GP for general population	99	75	60	43[2]
SMS	91	54	24	37
Needle Exchange Centres	61	48	104[3]	32.5
Pharmacies	77	22	21	39

[1] IgG positivity is intended as initial of the cascade of care, HCV+ detection is the end of the short-term model.
[2] Figure referring to the general population, counterfactual is the result of the average of the other three strategies with the general population.
[3] The higher number of reported disease stage observations is due to repeat assessments during the 2011–17 period.

net monetary benefit of each strategy.

Model structure

We used a deterministic model of HCV treatment and screening to compare the four different screening strategies in the Tayside area. The model comprised a short-term decision tree covering the first year and a Markov model extending it to a lifetime horizon.Theshort-term diagnosis outcomes fed into the long-term analysis (see Fig. 1). The economic analysis took the UK NHS perspective. The decision tree illustrates the HCV cascade of care: the propensity of going to a point of care (screening strategy), type of test offered, result delivery, and if antibody positive a confirmatory PCR test. The main differences across strategies over the short-term were: professional/personnel delivering the screening and type of test (dried blood spot (DBS) or venous sample), timing in delivering the confirmatory test and patients' characteristics (demographics and attrition across the HCV cascade of care). The outcome of the short-term analysis was the incremental cost per additional case detected.

A previously published Markov model (Younossi et al., 2015) was adapted and used to model the treatment and subsequent management pathway which, after screening, followed the natural history of HCV patients over a lifetime horizon. In the model, individuals who had been diagnosed with active HCV infection could be treated or could decline treatment/not respond. If successfully treated, individuals entered into the treatment arm achieving a sustained virologic response (SVR), where they had a much lower probability of progressive liver disease. Patients who were HCV positive but were either untreated, or the treatment failed, moved into the 'no treatment' arm (see Fig. 1). Patients who remained undetected in the short-term model also moved into the 'no treatment' arm in the Markov model, where the natural course of untreated HCV disease progresses (Fig. 1). Patients in both arms could enter the model from mild (stage F0) to severe fibrosis stages (stage F4) and could then potentially progress in the disease moving then further into decompensated cirrhosis (DCC); hepatocellular carcinoma (HCC); liver transplant (LT); post-liver transplant (LT + 1) and death. Outcomes for the lifetime analysis are reported in terms of the incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB), based on a willingness to pay threshold of £20,000 per quality-adjusted life year gained (QALY) (NICE 2012).

The different screening strategies determined the outcome of the short-term model (proportion of people detected and treated out of the total number of infected) and their average age at detection. Specifically, the observational data showed a significant difference in mean age of the people accessing the different screening strategies and, therefore, this was applied in the model (Table 1). Thus, all the strategies entered in the model at the same age (32 years, the average age of the population in the strategy with the earliest starting age) but started the screening according to their average age at detection. Disease stage progresses annually with transition probabilities in the model. Hence, strategies with higher average age of screening had a more advanced disease stage at detection (see Supporting Information for more details). A sensitivity analysis using observational data for the initial liver disease severity stage at the time of detection was undertaken (see supporting information and sensitivity analysis section). The length of each cycle in the Markov model was one year. After each cycle patients could remain in their state or change state in line with the model transition probabilities. As the long-term model is an extrapolation of the short-term results, the data coming from strategies' observations were limited to the aggregate demographics of the people screened. The treatment uptake rate, transition probabilities across Markov states, utility values for each state and mortality rates came from published literature relevant to the UK HCV population.

Parameters

Prevalence and transition probabilities

Data on the prevalence of current PWID used in the short-term model came from published literature (Dillon, Barclay, Fraser, & Hayes, 2018; Hutchinson, Bird, & Goldberg, 2005; Surveillance report. hepatitis c antibody positive cases in scotland: results to 31 december 2017, 2017) and experts' advice from clinicians involved in the Tayside model of care (Table 3). The probability of being screened and offered the test was also based on clinicians' opinion. Data on prevalence were derived from a combination of sources and adjusted to year 2017 according to the Health Protection Scotland epidemiology figures of the HCV trend rate over years (Surveillance report. hepatitis c antibody positive cases in scotland: results to 31 december 2017, 2017). This was validated by the clinicians involved in designing the strategies. The probability of every node following the offer or acceptance of the first test (IgG) was driven by observational data from the pilot strategies in Tayside, Scotland. The probability at every node was the proportion of people continuing in the cascade of care. Evidence for the PWID population screened at GPs was based on the average of the figures of the three strategies regarding PWID, with the data coming from the NHS Tayside general population and obtained from GP practices. Sensitivity and specificity of preliminary antibody tests depends on the type of test (a venous sample or DBS). The sample size of every strategy derived from observational data on the number of people tested and recorded in each strategy between 2015 and 2017.

Treatment, mortality and health utilities

HCV treatments applied in the model are the direct-acting antiviral (DAA) regimens recommended by Healthcare Improvement Scotland (Dillon, Barclay, Fraser, & Hayes, 2018). Overall, in Tayside the prevalence of HCV genotype 3 amongst the infected patients is assumed to be 70% and genotype 1 is 30%, in accordance with the local data. Treatment varies based on genotype and on being treatment naïve or experienced (Dillon, Barclay, Fraser, & Hayes, 2018). Treatment regimens were modelled as if all the patients were treatment naïve, a worst-case scenario where all patients were treatment experienced was considered in the sensitivity analysis. Background mortality in the Markov model wasadjusted with the standardised mortality ratio for the PWID population, in accordance with their lower life expectancy (Mathers et al., 2013). Parameters for HCV progression and health utilities for each Markov state were taken from previous published studies (using UK values) (Castelnuovo et al., 2006; McEwan, Kim, & Yuan, 2013; Younossi et al., 2018) (Table 3).

Table 3
Main input parameters.

Parameter	Mean value	Distribution	Source
Population characteristics			
PWID prevalence	0.43	Beta(α = 56.57,β = 74.9)	(Dillon, Barclay, Fraser, & Hayes, 2018; Hutchinson et al., 2005; Surveillance report. hepatitis c antibody positive cases in scotland: results to 31 december 2017, 2017)
Cascade of care			
PWID chance of going to GP	0.25	Norm(μ = 0.25,σ = 0.015)	Assumption
Chance of being screened for all the venues except GP	0.7	Norm(μ = 0.7,σ = 0.043)	Assumption
PWID GP - Chance of being tested if positive	0.20	Norm(μ = 0.2,σ = 0.012)	Assumption
IgG -Venous sample sensitivity	0.98		(Colin et al., 2001)
IgG -Venous sample specificity	0.99		(Colin et al., 2001)
DBS/oral fluid IgG sensitivity	0.92		(Colin et al., 2001; Judd et al., 2003)
DBS/oral fluid IgG specificity	0.99		(Judd et al., 2003)
GP Counterfactual- IgG + but PCR-	0.138	Beta(α = 12,β = 75)	NHS Tayside
GP Counterfactual- treatment acceptance	0.907	Beta(α = 68,β = 7)	NHS Tayside
GP Counterfactual- PCR acceptance	0.88	Beta(α = 88,β = 11)	NHS Tayside
SMS- IgG + but PCR-	0.18	Beta(α = 12,β = 54)	NHS Tayside
SMS- treatment acceptance	0.63	Beta(α = 45,β = 26)	NHS Tayside
SMS- PCR acceptance	0.73	Beta(α = 66,β = 25)	NHS Tayside
Needle Exchange- IgG + but PCR-	0.22	Beta(α = 6,β = 27)	NHS Tayside
Needle Exchange- treatment acceptance	0.76	Beta(α = 103,β = 32)	NHS Tayside
Needle Exchange- PCR acceptance	0.9	Beta(α = 27,β = 3)	NHS Tayside
Pharmacies- IgG + but PCR-	0.59	Beta(α = 50,β = 72)	NHS Tayside
Pharmacies- treatment acceptance	0.95	Beta(α = 21,β = 1)	NHS Tayside
Pharmacies- PCR acceptance	0.68	Beta(α = 49,β = 21)	NHS Tayside
Transition probabilities			
F0 to F1	0.117	Uniform ± 20%	(Coffin, Scott, Golden, & Sullivan, 2012; Thein, Yi, Dore, & Krahn, 2008)
F1 to F2	0.085	Uniform ± 20%	(Coffin et al., 2012; Thein et al., 2008)
F2 to F3	0.120	Uniform ± 10%	(Coffin et al., 2012; Thein et al., 2008)
F3 to F4	0.116	Uniform ± 20%	(Coffin et al., 2012; Thein et al., 2008)
F3 to HCC	0.002		(Coffin et al., 2012; McEwan et al., 2013; Thein et al., 2008)
F4 to HCC	0.014	Beta(α = 1.93,β = 136.11)	(McEwan et al., 2013; Younossi et al., 2018)
F4 to DC	0.039	Beta(α = 14.62,β = 360.17)	(Martin et al., 2012, 2016)
DC to HCC	0.014	Beta(α = 1.93,β = 136.11)	(Martin et al., 2012, 2016; Younossi et al., 2018)
DC to LT	0.030	Beta(α = 6.53,β = 210.99)	(Martin et al., 2012)
DC to D	0.130	Beta(α = 147.03,β = 983.97)	(Martin et al., 2012)
HCC to LT	0.103		(McGarry et al., 2012; Martin et al., 2012)
HCC to D	0.427	Beta(α = 117.1,β = 155.23)	(McGarry et al., 2012; Martin et al., 2012; Younossi et al., 2018)
LT to D	0.210	Beta(α = 16.28,β = 61.23)	(Martin et al., 2012)
LT1 to D	0.057	Beta(α = 22.9,β = 378.88)	(Martin et al., 2012)
SVR-F3 to SVR F2	0.267		(Younossi et al., 2015)
SVR-F4 to SVR F3	0.076		(Younossi et al., 2015)
SVR relative risk F4 to HCC[a]	0.24		(Morgan et al., 2013; Younossi et al., 2015)
SVR relative risk F3 to HCC[a]	0.24		(Morgan et al., 2013)
SVR relative risk F4 to DC[a]	0.086		(Morgan et al., 2013)
Treatment success, genotype 1 (F0-3)[a]	0.97		(Ahmed et al., 2018)
Treatment success, genotype 1 (F4)[a]	0.95		(Ahmed et al., 2018)
Treatment success, genotype 3 (F0-3)[a]	0.98		(Foster et al., 2015)
Treatment success, genotype 3 (F4)[a]	0.93		(Foster et al., 2015)
Utilities			
F0-F1	0.77	Beta(α = 521.24,β = 155.69)	(Martin et al., 2012)
F2-F3	0.66	Beta(α = 168.25,β = 86.87)	(Martin et al., 2012)
F4	0.55	Beta(α = 521.24,β = 155.69)	(Martin et al., 2012)
HCC	0.45	Beta(α = 123.75,β = 151.25)	(Martin et al., 2012)
DC	0.45	Beta(α = 123.75,β = 151.25)	(Martin et al., 2012)
LT	0.45	Beta(α = 123.75,β = 151.25)	(Martin et al., 2012)
SVR F0-F1	0.82	Beta(α = 65.87,β = 14.46)	(Martin et al., 2012)
SVR F2-F3	0.72	Beta(α = 58.06,β = 22.28)	(Martin et al., 2012)
SVR F4	0.61	Beta(α = 58.05,β = 37.11)	(Martin et al., 2012)
Main Short term unit cost (£ per patient)			
Dried blood spot test	11.55		NHS Tayside(2018)
PCR test	50.25		NHS Tayside(2018)
IgG venous blood sample	12.50		NHS Tayside(2018)
Specialist nurse time	15.25		(Curtis & Burns, 2017)
GP consultation time	28.00		(Curtis & Burns, 2017)
Costs (£ per year)			
DC	12,234	PPIxGamma(α = 36.02,β = 253.16)	(Castelnuovo et al., 2006)
HCC	10,904	PPIxGamma(α = 18.11,β = 448.8)	(Castelnuovo et al., 2006)
LT	36,664	PPIxGamma(α = 89.75,β = 304.5)	(Castelnuovo et al., 2006)
LT + 1	1858	PPIxGamma(α = 15.22,β = 91.01)	(Castelnuovo et al., 2006)
F4 treated people monitoring expenses	284		NHS reference costs for Ninewells procedures
Treatment costs per cycle			
Gen1-cirrhotic	36,500		BNF,2019 prices

(*continued on next page*)

Table 3 (*continued*)

Parameter	Mean value	Distribution	Source
Gen1-noncirrhotic	36,500		BNF,2019 prices
Gen3-cirrhotic	39,740		BNF,2019 prices
Gen3-noncirrhotic	25,987		BNF,2019 prices
Standardised mortality ratio for PWID	14.68		(Mathers et al., 2013)

[a] Treatment success rate and relative risk parameters do not have distributions, and they were added with no uncertainty into the PSA

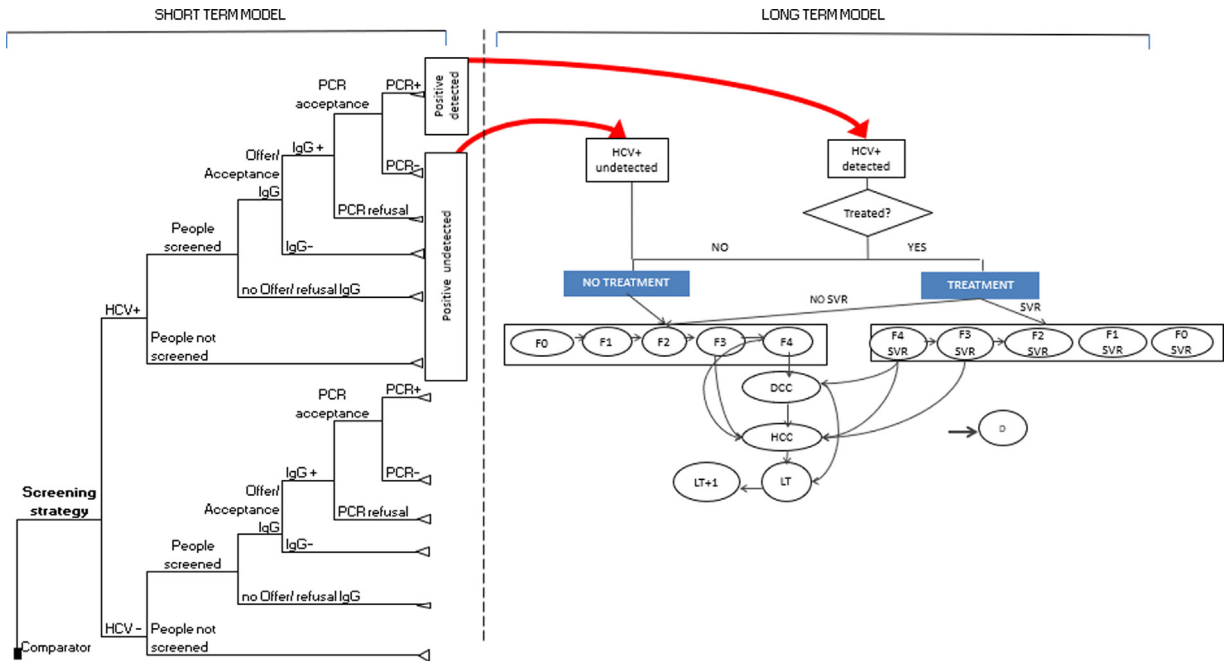

Fig. 1. Short term decision tree & lifetime Markov Model. Markov model structure taken from (Younossi et al., 2018) and adapted to this study. Short term model: IgG = preliminary test to detect HCV antibodies. Individuals can be IgG positive, but they can clear on their own the virus resulting PCR negative (therefore not infected). PCR = confirmatory test. Long term model: DCC = decompensated cirrhosis, D = death, F0-4 = metavir score (liver fibrosis stage) in ascending order of severity, HCC = hepatocellular carcinoma, LT = liver transplant, LT + 1 = after one year of liver transplant, SVR = sustained virologic response.

Costs

Cost data were obtained directly from Ninewells Hospital (Tayside) and NHS Reference costs in accordance with Ninewells procedures. Costs included in the model are those relevant from the UK NHS perspective. This comprised the cost of screening, equipment, testing, treatment and monitoring (Table 3). All costs were adjusted to 2017 prices and discounted annually at 3.5% (NICE 2012). Patients detected and treated at F0, F1, F2 or F3 do not incur further costs. Following treatment patients detected at F4 were assumed to be monitored annually, in accordance with Ninewells Hospital (Tayside) procedures. Scottish national guidelines (Dillon, Barclay, Fraser, & Hayes, 2018) determined the treatment used in the model. Treatment cost was obtained from the British National Formulary. In line with the original model (Martin et al., 2012), individuals with undetected or detected but not treated HCV, were assumed to have no treatment related costs in the model until reaching decompensated cirrhosis. This is the stage when liver disease becomes severe and symptomatic and therefore, patients are assumed to receive care.

Sensitivity analysis

A Probabilistic Sensitivity Analysis (PSA) was undertaken using 1000 iterations Monte Carlo Simulation in which all key parameter inputs to the model were randomly sampled from a predefined probability distribution. The probability distributions mean values and standard errors used for the PSA for the parameters are reported in Table 3. One-way sensitivity analyses were also performed on the following parameters to evaluate further the impact of uncertainty in assumptions and other areas on results:

- 0–100% discount applied to the list price of HCV drug treatments.
- Assumption of 100% treatment uptake after diagnosis.
- 100% increase in offering IgG test by GPs.
- 50% decrease in initial prevalence.
- Substitution of the model diseases stage prevalence at detection with the observable data.
- Same age (32 years) and same initial stage of disease across all the strategies.
- Treatment regimens assuming all patients were treatment experienced.
- The different likelihood of going to a specific screening site for PWIDbased on the number of positive PCR collected in each screening setting from 2015 to 2017.

Scenario analysis

The PWID population has a high risk of re-infection due to their high risk lifestyle (needle and syringe sharing) (Falade-Nwulia, Sulkowski, Merkow, Latkin, & Mehta, 2018; Schulkind et al., 2019), yet re-infection rates are uncertain and vary based on a variety of risk factors. To account for reinfection in the model, a scenario analysis was undertaken whereby an additional transition probability was introduced from the SVR states to the same non-treated state for all the PWID strategies. In effect, this means that after incurring the cost of

Table 4a
Short- and long-term results- pairwise comparison (every strategy vs current practice).

Short term						
Strategy	**Expected Strategy cost £**	**Proportion of detected (% out of total positive)**	**Cost per positive detected**	**Incremental cost £**	**Incremental Effect**	**ICER**
GP PWID	5.61	0.02 (3.9%)	335.07			
SMS	15.08	0.10 (23.4%)	149.82	9.47	8.4%	112
Needle Exchange	19.11	0.12 (28.9%)	152.98	13.49	10.8%	124
Pharmacies	22.91	0.09 (21.9%)	242.16	17.30	7.8%	222
Long term						
Strategy	**Cost £ (95% Cred Inter.)**	**QALY (95% Cred Inter.)**	**Incremental cost**	**Incremental QALY**	**ICER**	**NMB (£)**
GP PWID	5143 (3327,7591)	8.29 (7.93,8.66)	–	–	–	160,737
SMS	8032 (5692,10,190)	8.42 (8.05,8.78)	2889	0.13	22,518	160,414
Pharmacies	9321 (7012, 11,320)	8.44 (8.09,8.79)	4178	0.15	27,402	159,609
Needle Exchange	10,117 (7532,11,787)	8.70 (8.31,9.04)	4974	0.40	12,336	161,814
Reinfection scenario						
GP PWID	5162 (3333,7608)	8.29 (7.91,8.62)	–	–	–	160,589
SMS	8156 (5758,10,371)	8.37 (8.00,8.74)	2995	0.08	35,813	159,267
Pharmacies	9465 (7104,11,526)	8.40 (8.04,8.76)	4304	0.11	39,969	158,439
Needle Exchange	10,369 (7629,12,140)	8.47 (8.07,8.82)	5207	0.19	28,000	159,102

ICER = Incremental Cost-Effectiveness Ratio, NMB = Net Monetary Benefit, QALY = Quality Adjusted Life Years. NMB calculated using a willingness to pay of £20,000/QALY. NMB= [Effectiveness*(Willingness to pay)-Costs]. Due to rounding, Figures throughout the table may not add up to the totals. There may be discrepancies between the reported ICER, NMB and those totals

treatment, some patients were then immediately re-infected and continue to progress in the model as if they had received no treatment. It was assumed that once an individual was re-infected after treatment, the individual did not receive further treatment in the future. The re-infection rate adopted for this scenario was based on the most recent data on HCV re-infection for PWID in Tayside (Rossi et al., 2018). This study mapped reinfection within the same needle exchange centre analysed for the study. To account for a lower reinfection risk in older individuals (Rossi et al., 2018) (and the consequent reduction in sharing propensity), the transition probability of reinfection used was assumed to decrease over time in accordance with the data (Rossi et al., 2018). The reinfection rate at 33 years was 0.10 (average age of screening at needle exchange pathway), and at 40 years was 0.06 (age for PWID going to GP). The rate of re-infection decreased on an average of 7.5% per year.

Results

Offering tests at needle exchange centres was associated with a 10% (7.45-fold) increase in cases detected compared to the standard care (Table 4a). Whereas, for SMS and pharmacies the increase was 8.4% and 7.8%, respectively. Whilst the needle exchange strategy cost £13 per case detected more than screening at GP practices, the most expensive strategy was screening at pharmacies at £17.30 and the cheapest was SMS with £9.47. The highest and lowest strategies in terms of cost per HCV+ detected are a symptomatic screening at GPs (£335) and screening at SMS (£150), respectively. Screening at SMS cost £112 per any additional person screened compared to GP. Screening at needle exchange services had an ICER of £124 per additional HCV+ detected against GP. Each strategy had a low ICER value and could be considered cost-effective compared to the GP current practice in a pairwise comparison. Using an incremental approach (Table 4b), screening at SMS was the most cost-effective strategy in the short term.

The results in the long-term differ from the short-term. Indeed, looking at the cost per QALY in a life time horizon rather than at the cost per case detected, needle exchange was the most cost-effective alternative setting to a screening at GPs. This is because the proportion of positively detected HCV cases incurred costs, quality of life and life expectancy implications over the patient lifetime. In the lifetime analysis only screening at needle exchange was cost-effective with an incremental cost-effectiveness ratio value of £12,336/QALY,generating the greatest QALY gain (0.4 QALYs) in the population due to a higher number of people treated compared to its comparator. Based on the incremental analysis, both SMS and pharmacies were dominated by needle exchange and GP.

Sensitivity & scenario analyses

The results of the PSA suggest that screening at needle exchange was highly likely to be a cost-effective strategy. However, there was considerable uncertainty surrounding the cost-effectiveness of both screening at pharmacies and SMS, respectively, depending on the chosen willingness to pay (WTP) for QALY gains (Fig. 2) (CEAC in Supporting Information).

Assuming all strategies began screening at the same age (32 years) and, with the same disease severity, made both SMS and Pharmacy strategies cost-effective, bringing them below the £20,000/QALY threshold (Fig. 3b). Alternative assumptions regarding the probability of going to a different point of care based on the number of PCR+, as well as having a 100% treatment uptake, had little impact on the cost-effectiveness results. Using the observed value for disease severity at detection made all the strategies cost-effective at less than £5000/QALY compared to the screening at GP (Fig. 3b). An increase in treatment price, such as using a worst-case scenario where allindividuals were treatment experienced and require costlier treatments, led to screening at needle exchange being the only cost-effective strategy (Fig 3b). However, if a 24% discount on the UK list price of treatments was applied, there was the potential for all strategies to be considered cost-effective. (Fig. 3a).

When reinfection rates were introduced to the base case model, all strategies were not cost effective at a threshold of £20,000 per QALY.

Discussion

In this study we compared each of the three HCV screening strategies both individually and incrementally against the current practice. To the best of our knowledge, this is the first time that data coming from multiple current vanguard screening strategies have been compared to shed light on how current screening policies are performing in tackling HCV from a health economic perspective. We found that novel strategies for targeting and screening PWID populations are likely to be cost-effective compared to current standard care.

While screening at needle exchange resulted in the highest number of cases being detected, the lowest cost per case detected was associated with SMS. Hence, screening at SMS was the most cost effective

Table 4b
Short- and long-term results- incremental comparison.

Short term						
Strategy	**Expected Strategy cost £**	**Proportion of detected (% out of total positive)**	**Cost per positive detected**	**Incremental cost £**	**Incremental Effect**	**ICER**
GP PWID	5.61	0.02 (3.9%)	335.07			
Pharmacies	22.91	0.09 (21.9%)	242.16	Strictly dominated by SMS		
SMS	15.08	0.10 (23.4%)	149.82	9.47	0.08	118.38
Needle Exchange	19.11	0.12 (28.9%)	242.16	4.03	0.02	201.05
Long term						
Strategy	**Cost £ (95% Cred Inter.)**	**QALY (95% Cred Inter.)**	**Incremental cost**	**Incremental QALY**	**ICER**	**NMB (£)**
GP PWID	5143 (3327,7591)	8.29 (7.93,8.66)	–	–	–	
SMS	8032 (5692,10,190)	8.42 (8.05,8.78)	extended dominated by Needle Exchange and GP PWID			
Pharmacies	9321 (7104,11,526)	8.44 (8.09,8.79)	strictly dominated by SMS			
Needle Exchange	10,117 (7532,11,787)	8.70 (8.31,9.04)	4974	0.4	12,336	161,814
Reinfection scenario						
GP PWID	5162 (3333,7608)	8.29 (7.91,8.62)	–	–	–	
SMS	8156 (5758,10,371)	8.37 (8.00,8.74)	extended dominated by Needle Exchange and GP			
Pharmacies	9465 (7104,11,526)	8.40 (8.04,8.76)	extended dominated by Needle Exchange and GP			
Needle Exchange	10,369 (7629,12,140)	8.47 (8.07,8.82)	5207	0.19	28,000	159,102

Pairwise comparison	Probability of being cost effective at different willingness to pay thresholds					
	£0	£10,000	£20,000	£30,000	£40,000	£50,000
Needle exchange GP	0% 100%	22% 88%	98% 2%	100% 0%	100% 0%	100% 0%
Pharmacies GP	0% 100%	0% 100%	5% 95%	62% 38%	88% 12%	95% 5%
SMS GP	0% 100%	0% 100%	29% 61%	83% 17%	95% 5%	99% 1%

Fig. 2. Incremental cost effectiveness plane with all the strategies against the current standard practice - Base case scenario. Table represent the probability of being cost effective for every strategy against the current standard practice (GP) at different willingness to pay.

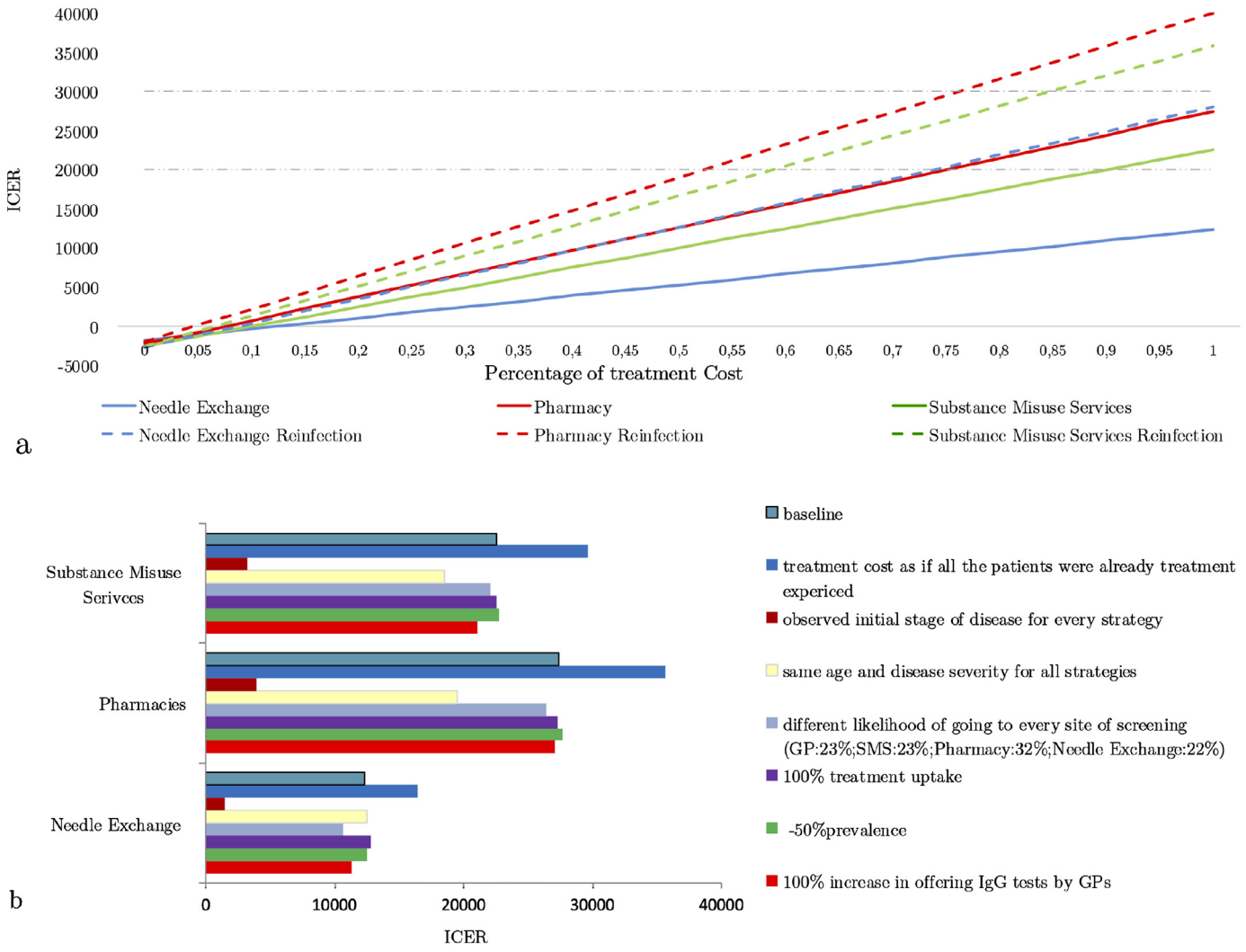

Fig. 3. 3a. Line chart illustrating ICER for screening by the percentage of treatment listed price for baseline and re-infection scenario. 3b. One-way sensitivity analysis.

approach to detect current PWID positive patients, followed by screening at needle exchange services. Indeed, these strategies, which rely on mostly non-clinician personnel are typically less costly. Although in the long term the higher number of people screened and detected incurred greater costs, screening current PWID at needle exchange remained cost-effective. The difference in cost-effectiveness across strategies between short and lifetime horizon was mainly due to disease stage, which was accounted for in the long term. This suggests that screening at an older age, which is more likely in strategies involving SMS and pharmacies, detects disease at more severe stages and, therefore, with more advanced liver damage and lower quality of life after treatment. Screening intensification at GPs for current PWID would increase both the number of people detected, but also the overall cost of the strategy in the short-term. However, even if more people were screened, the average older age of screening would increase the cost of treatment more than the potential gain in QALY in the long term (see long term sensitivity analysis, Fig. 3b). Nevertheless, age was not the sole driver of the cost-effectiveness results in the lifetime model: holding age constant across different strategies, standard screening at the GPs remained the least effective alternative due to the lower detection rate coming from the short-term model (see sensitivity analysis).

In the reinfection scenario, only screening at needle exchange centres was below £30,000/QALY. This may be the result of our data coming from a small sample that reported higher reinfection rates than previous publications (Aspinall et al., 2013; Dimova et al., 2013). Moreover, the reinfection model was designed to consider only treated individuals who could be re-infected if sharing injecting equipment with those who are infected, reducing the cost-effectiveness in the model. However, given the model's static framework, it did not consider that augmenting the number of treated individuals in a population would reduce the pool of potential HCV positive people spreading the infection. A possible change in the propensity of sharing needles after treatment was not taken into account either. In a dynamic scenario, both these last two effects could potentially counterbalance the previous. We suggest that the outcome of our reinfection scenario should be interpreted as an extremely conservative scenario. It is reasonable to expect that with these policies the overall HCV prevalence within the PWID population will decrease. Our results show that changes in prevalence would impact mainly short-term dynamics, but not affect long term conclusions (Fig 3b).

All the strategies involved the same macro population and belonged to the same model of care piloted and performed in Tayside. However, it is reasonable to expect that different screening sites could identify different subpopulations, which do not necessarily overlap. For instance, the regular client of a pharmacy is likely to have a different profile than the needle exchange frequenter (same reasoning for SMS). Unfortunately, the lack of data, in particular regarding the PWID access to differing points of care, means that we were unable to track the

different clients' profile. Thus, we analysed the PWID population as if it was homogeneous across strategies. The result was that screening at needle exchange was the most cost-effective option. Nevertheless, there will likely be challenges for the implementation of screening through a single strategy, such as capacity constraints at a single point of care, individuals' preferences or the availability of a specific test setting, and hence complementary strategies should be considered. To allow for more comprehensive policy suggestions based on observational evidence, governments should invest in data collections across local PWID community services (e.g. to map different client profiles to estimate the weight of every strategy within the model of care) to provide stronger evidence of every strategy's characteristics at local levels. Policymakers should run central policies which include a mix of the most cost-effective approaches reflecting the availability of specific points of care and the prevalence of user profile in a specific area.

The sensitivity analysis of the treatment list price shows that the main driver for the cost-effectiveness analysis is the treatment cost. In Scotland and many other regions and countries there is a nationally published list price for HCV medications, and from these there are confidential negotiations that reduce the costs dependant on volume of sales and other factors. From personal communications reductions in costs are the norm and in the HCV field they are well in excess of 50%. Therefore, analyses with discounted drug prices on the official listed price by the UK British National Formulary (BNF 2019) should be a more realistic representation of the costs in clinical practice. In this regard, a discount of 24% of the treatment listed price made all the strategies in each scenario cost-effective at a £20,000 WTP threshold. For the re-infection scenario, at discount equal to or greater than 48% made all strategies cost-effective. Given the importance of treatment price in our analyses, in countries where the actual HCV treatment price is still high for the health care providers, further negotiation with the industry is crucial to reach sustainable cost-effectiveness strategies. In contexts where this interaction between stakeholders already happens, such as in Scotland where reductions in list costs are the norm, screening strategies are likely to be cost-effective. Hence, the focus of policymakers should be more on stratagems to detect individuals at early stage of disease, improving engagement within the cascade of care and limiting reinfection.

Strengths and limitations

This study sought to evaluate the cost-effectiveness of the current and potential new approaches to tackle HCV detection. Our findings confirm that alternative strategies to detect positive PWID can be highly cost-effective. Specifically, approaches that detect at earlier stages of infection (which is likely to mean younger individuals) and capture a higher number of individuals are expected to be the most cost-effective. However, there were also several limitations to our study.

Firstly, the representativeness of the model of care is unclear as it was based on a small sample of potential screening locations and on a sample of the drug-user population in the Tayside area. Moreover, this was a retrospective study using for the first time a multitude of strategies from a relatively small area. Even if these findings can provide insights to policy makers, results may have a local perspective. For national recommendations, prospective cohort studies need to be implemented, which could overcome the potential bias affecting the selection of our counterfactual. In this regard, given the need to reflect regional differences, central policies should be tailored on evidence from a local level.

Secondly, the lack of data on a few key parameters, such as the proportion of people visiting the different screening sites, led to the use of secondary data sources. Unfortunately, there is currently limited data available on some community services. Therefore, our HCV test acceptance/offer rate was based on expert and clinical opinions of personnel working within the services described in our study. However, this was addressed by testing our assumptions in one-way sensitivity analyses and using wide uncertainty in the PSA.

Thirdly, the reinfection scenario analysis did not take into account a herd immunity factor. Indeed, in small areas, there could be a decrease in incidence since treating people reduces the number of infected people able to transmit the infection. However, it should be noted that usually the reinfection rate is not modelled in screening models and, when it is, it can be very sensitive to authors' assumptions (Geue et al., 2015). We decided to include the prospect of reinfection in a scenario analysis in a static setting. As already mentioned, our reinfection model should be interpreted as an extremely conservative scenario.

Lastly, the model was static and, beyond reinfection, it did not allow for a migration from the PWID status. However, the lack of data regarding this potential transition, the fact that these were retrospective cohorts referring to heterogeneous samples, and the desire to provide a snapshot of an ongoing policy in its first years of operation, led us to build a static model in line with most of the recent literature on cost-effectiveness of HCV treatment (Chhatwal, He, & Lopez-Olivo, 2016) and screening (Geue et al., 2015). Since the static nature of the analysis does not allow direct assessment of the cost-effectiveness of the strategies over time, a plausible decrease in prevalence due to these policies was considered in the sensitivity analysis.

This study presents a comprehensive analysis of a regional HCV screening strategy in the UK and provides insights that need to be addressed to ensure cost-effective decision-making at a national level. For instance, treatment cost has a crucial role in determining whether screening strategies targeting a PWID population are likely to be cost-effective. Overall, the cost-effectiveness of a strategy increases in the short-term with the engagement in the cascade of care, and in the long term with early diagnosis (associated with a point of care screening at younger ages) and treatment cost. In Tayside, screening at all the alternative screening sites seems to respect these requirements. Our results found that screening at needle exchange was likely to be the most cost-effective strategy in the long-term. Indeed, with the application of a plausible discount to the treatment price, the study demonstrates how all the screening strategies could be considered highly cost-effective when compared to the current standard care in the UK. Whilst these results are specific to the Tayside region, the study highlights that there is a need for further investigation to understand how these strategies would perform elsewhere. Governments wishing to achieve the 2030 HCV elimination target must shape central policies based on the effectiveness and cost-effectiveness of different screening strategies at a sub-national level. They should, therefore, invest in further research to enable extensive data collection across regions thus allowing for more comprehensive, tailored and cost-effective decision-making.

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Author contributions

FM and KB designed the economic evaluation. FM analysed data and drafted the manuscript. KB supervised the analysis and reviewed the manuscript. KB, JD designed the study. JD and ER coordinated the study, collected the data and reviewed the final manuscript.

Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.drugpo.2020.102811.

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