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Cost effectiveness of an intervention to increase uptake of hepatitis C virus testing and treatment (HepCATT): cluster randomised controlled trial in primary care

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ABSTRACT OBJECTIVE

To evaluate the effectiveness and cost effectiveness of a complex intervention in primary care that aims to increase uptake of hepatitis C virus (HCV) case finding and treatment.

DESIGN

Pragmatic, two armed, practice level, cluster randomised controlled trial and economic evaluation.

SETTING AND PARTICIPANTS

45 general practices in South West England (22 randomised to intervention and 23 to control arm). Outcome data were collected from all intervention practices and 21/23 control practices. Total number of flagged patients was 24 473 (about 5% of practice list).

INTERVENTION

Electronic algorithm and flag on practice systems identifying patients with HCV risk markers (such as history of opioid dependence or HCV tests with no evidence of referral to hepatology), staff educational training in HCV, and practice posters/leaflets to increase patients' awareness. Flagged patients were invited by letter for an HCV test (with one follow-up) and had on-screen pop-ups to encourage opportunistic testing. The intervention lasted one year, with practices recruited April to December 2016.

MAIN OUTCOME MEASURES

Primary outcome: uptake of HCV testing. Secondary outcomes: number of positive HCV tests and yield

(proportion HCV positive); HCV treatment assessment at hepatology; cost effectiveness.

RESULTS

Baseline HCV testing of flagged patients (six months before study start) was 608/13 097 (4.6%) in intervention practices and 380/11 376 (3.3%) in control practices. During the study 2071 (16%) of flagged patients in the intervention practices and 1163 (10%) in control practices were tested for HCV: overall intervention effect as an adjusted rate ratio of 1.59 (95% confidence interval 1.21 to 2.08; $P<0.001$). HCV antibodies were detected in 129 patients from intervention practices and 51 patients from control practices (adjusted rate ratio 2.24, 1.47 to 3.42) with weak evidence of an increase in yield (6.2% v 4.4%; adjusted risk ratio 1.40, 0.99 to 1.95). Referral and assessment increased in intervention practices compared with control practices (adjusted rate ratio 5.78, 1.6 to 21.6) with a risk difference of 1.3 per 1000 and a "number needed to help" of one extra HCV diagnosis, referral, and assessment per 792 (95% confidence interval 558 to 1883) patients flagged. The average cost of HCV case finding was £4.03 (95% confidence interval £2.27 to £5.80) per at risk patient and £3165 per additional patient assessed at hepatology. The incremental cost effectiveness ratio was £6212 per quality adjusted life year (QALY), with 92.5% probability of being below £20 000 per QALY.

CONCLUSION

HepCATT had a modest impact but is a low cost intervention that merits optimisation and implementation as part of an NHS strategy to increase HCV testing and treatment.

TRIAL REGISTRATION

ISRCTN61788850.

Introduction

Hepatitis C virus (HCV) infection, predominantly transmitted by exposure to blood, is a major cause of chronic liver disease and cirrhosis.^{1 2} More than 100 000 people in England are estimated to have chronic HCV infection, and more than 85% of these infections were acquired through injecting drug use.³

Chronic HCV infection can now be cured in more than 95% of patients with a range of highly tolerable, single pill a day, short regimen (8-12 weeks) direct acting antiviral agents.⁴⁻⁶ Consequently, the World Health Organization developed a strategy to eliminate HCV as a public health threat,⁷ setting targets for

WHAT IS ALREADY KNOWN ON THIS TOPIC

Chronic hepatitis C virus (HCV) infection can now be cured in more than 95% of patients

HCV case finding is critical for NHS England to increase HCV treatment and eliminate HCV as a public threat by 2025, five years before the WHO target

Economic models and guidance recommending increasing HCV testing for at risk patients in primary care are not based on robust evidence

WHAT THIS STUDY ADDS

HepCATT is complex intervention based around an electronic algorithm integrated with primary care practice systems that identifies and flags patients with risk markers of HCV infection

HepCATT can increase HCV case finding by a modest amount and be highly cost effective

The intervention would benefit from being optimised before implementation across UK primary care

decreasing the incidence of HCV by 80% and HCV related mortality by 65% by 2030.⁸ NHS England aims to achieve the WHO goals by 2025.

Since 2016 more than 10 000 people a year have been treated for HCV and an estimated 50 000 people have been diagnosed as having it, although many of these may not have been assessed or be under management by HCV services.³⁻⁹ Primary care is the largest source of HCV testing, comprising nearly 30% of all HCV antibody positive tests in laboratory surveillance.¹⁰

The UK's National Institute for Health and Care Excellence (NICE) suggests that interventions to increase case finding in drug treatment centres and primary care are likely to be cost effective.¹¹ However, robust evidence from randomised controlled trials on such interventions is lacking, and rates of case finding and drug treatment at many sites are low.¹²⁻¹³ For instance, NICE's recommendations and economic models were based on a small uncontrolled study in eight practices (selected from areas of high deprivation and high prevalence of injecting drug use).¹⁴

We sought to update the evidence on HCV case finding in primary care and conduct a cluster randomised controlled trial, at general practice level, to establish whether a complex intervention to identify and invite patients at high risk of HCV was effective and cost effective at increasing HCV case finding and referral of people with HCV disease for assessment at specialist services.

Methods

HepCATT (Hepatitis C Assessment Through to Treatment Trial) was a pragmatic, two armed, practice level, cluster randomised controlled trial carried out in general practices in the South West of England with both qualitative and economic evaluation components.¹⁵ The nested qualitative study is reported separately.¹⁶

Randomisation

General practices were the unit of allocation and were randomised by an independent statistician in a 1:1 ratio to either receive the intervention or continue care as usual (control group). Randomisation was stratified by area (Bristol and non-Bristol, in case differences existed at baseline between city and semi-rural practices) and minimised by current rate of HCV testing as measured by Public Health England laboratory surveillance (high ($\geq 1\%$ of practice list) versus low ($< 1\%$)) and practice size.¹⁰ Minimisation retained a random element such that each practice being allocated was more likely to be, but was not inevitably, allocated to the group that achieved the best balance in HCV testing and practice size between intervention and control groups. Of 93 practices in our target area, 15 (16%) had high HCV testing rates.

Intervention

The intervention (registered: <http://www.isrctn.com/ISRCTN61788850>) follows NICE recommendations.¹⁷ It is described in more detail in our protocol¹⁵ (and in

the supplementary material). In brief, the intervention had multiple components. (1) HCV audit tool and patient flag: we designed a new algorithm for the Audit+ software (Informatica Systems Ltd), which is fully integrated with primary care systems once installed in practices and would identify and flag patients with high risk HCV markers (see supplementary material for a full list of risk markers and associated Read codes). The audit tool automatically aims to exclude any patients tested less than one year previously who were negative for HCV antibodies, referred to hepatology, receiving low doses of buprenorphine and methadone for pain management, or at end of life. (2) Training was provided in use of the HCV audit tool. We recommended that practices should first screen their list of patients and exclude on the system any patient for whom they thought that an invitation for HCV testing or discussion of treatment was not appropriate. Then eligible patients should be offered HCV testing either opportunistically (responding to on-screen pop-ups) or through encouragement to book an HCV test by letter generated automatically by the software (see supplementary material). We also recommended that patients should be followed up to arrange appointments. (3) Educational training: practice staff were encouraged to make use of free online HCV educational resources (eg, Royal College of General Practitioners e-learning module: <https://elearning.rcgp.org.uk/>). (4) Raising patients' awareness: information posters and leaflets, produced by the HCV Trust, were provided to practices. (5) Clinical history: practices were encouraged to add a question about injecting drug use to their new patient registration.

Practices delivered this intervention over a 12 month study period. Patients with a positive antibody test were managed according to local practice, which would be referral to specialist services unless contraindications were present. Practice start date varied from April to December 2016.

Control practices continued to do opportunistic HCV case finding as usual. We contacted control practices only at the time of randomisation and at the end of the intervention period when we asked them to install and run the same HCV audit to generate outcome data. The control practices also were given a one year licence for the Audit+ software.

Outcomes

The main outcome was uptake of HCV testing. The secondary outcomes were yield (number of HCV positive tests and proportion of HCV tests that were positive), and referral and assessment for treatment of patients with chronic HCV at hepatology.

We collected outcomes and data on patients' risk profile from general practices by using the Audit+ software in the intervention practices and control practices and linked them, using patient identifiers, with Public Health England laboratory data on HCV test results (HCV antibody and polymerase chain reaction). We identified patients assessed in hepatology by linking HCV tests—that is, a viral load test in secondary care

following both positive HCV antibody and polymerase chain reaction tests in primary care (validated previously as a measure of HCV treatment referral and assessment¹⁸)—for our final report to funders. This was a change from our protocol in relation to secondary care to save time because of delays in obtaining data from controls owing to changes in research governance. We subsequently confirmed assessment through linkage between the laboratory and specialist services. In a sensitivity test, we linked HCV antibody tests in primary care to polymerase chain reaction tests in secondary care, as some polymerase chain reaction tests in primary care were missing.

Sample size calculation

In our original calculation, we assumed that an average practice would have a list of 4225 adult patients aged 15-65 years, of whom approximately 1% (n=42) would have an injecting drug history, and that 40% (n=17) of these would be HCV positive. We consequently assumed that at least 10 patients would be identified as at high risk in each practice. We assumed an intra-cluster correlation coefficient of 0.05 and hence a design effect of 1.45 to accommodate variation in antibody testing rates across practices. We needed, therefore, a sample size of 46 practices (23 intervention and 23 control; 230 patients at high risk identified in each arm) to detect a true absolute difference in HCV antibody testing uptake of 12% (from 5% to 17% of patients at high risk identified), with 90% power at the 5% significance level.^{14 19}

Statistical analysis

The trial cohort comprised those patients identified as at high risk by the HCV audit tool. Analyses followed the intention to treat principle, with practices being analysed in the groups to which they were randomly allocated. We used Stata statistical software version 15.1 for all analyses. The primary analysis was pre-specified before collection of the outcome data.¹⁵ We estimated the proportion of patients with high risk markers tested for HCV antibodies, compared between intervention and control arms as a rate ratio, in a random effects Poisson regression model (random effects assumed to be normally distributed), adjusted for potentially prognostic variables used to stratify the random allocation (site of practice, HCV testing rate at baseline). This regression model accommodated any additional variation in the outcome measure between practices by incorporating an extra parameter and also allowed for the shorter follow-up period at two practices by including practice follow-up time as an offset term. The use of a mixed effects Poisson model is a variation to the analysis pre-specified in the protocol,¹⁵ in which we stated that we would be using negative binomial regression. Mixed effects Poisson regression models, by allowing a multi-level model, more easily accommodate covariates at both the practice and individual levels. Both approaches are elaborations of Poisson regression, the key difference being that the negative binomial

model assumes a γ distribution of testing rates across practices. In fact, the observed distribution of antibody testing rates was closer to a γ distribution than to a normal distribution, but repeating the analyses with practice level covariates using each of the two methods in turn gave practically identical results. We adapted this approach to the secondary outcome measures. The model was extended with the addition of an interaction term to compare the effect of the intervention on the primary outcome between subgroups specified in terms of being at high risk owing to opioid dependence/ injecting drug use or being at high risk owing to one of the other factors (exploratory analysis). We present a crude estimate of the risk difference for the primary outcome with 95% confidence interval (calculated by making the normal approximation), with, at the suggestion of a reviewer, an adjusted risk difference estimated using Stata's `adjrr`.²⁰

Economic analysis

Our economic evaluation first estimated the cost per HCV test and referral from the trial and practice perspective and then estimated the cost per quality adjusted life year (QALY) gained associated with the intervention by using an existing Markov model.^{21 22} Both analyses were performed from the NHS perspective, with results presented in pounds sterling in 2017. Full details of the economic evaluation methods are given in our protocol¹⁵ and supplementary material.

Briefly, for the within trial analysis, we compared costs between intervention and control practices by using mixed effects linear regression, clustered by practice, adjusting for sampling stratification and length of follow-up. We estimated the cost of HCV case finding per patient at high risk identified through the HCV algorithm and calculated the incremental cost per patient assessed at secondary care in intervention versus control practices. We used a cost effectiveness acceptability curve to explore uncertainty.²³ In a second analysis, we removed the costs and the Audit+ installation, training, and maintenance costs, as Audit+ is now routinely available to general practices with much wider functionality than just HCV case finding.

In the economic model, we compared the HepCATT intervention versus current practice, using a Markov model over a lifetime time horizon. We assumed that the intervention was implemented for one year in a static cohort. The model produces incremental cost effectiveness ratios (ICERs) per QALY gained, with both costs and QALYs discounted at 3.5%,²⁴ and estimates the probability of cost effectiveness at a willingness to pay threshold of £20 000 per QALY for the NHS. We did multiple scenario and sensitivity tests (excluding training costs; assuming lower health utility values associated with opioid dependent people; assuming linkage to care for each arm was equal; halving estimated HCV direct acting antiviral treatment cost to £5000 per course). We also did a "threshold analysis" to estimate the minimum increase in HCV antibody

testing needed for the intervention to remain cost effective. Table 1 shows the economic inputs.

Patient and public involvement

During the set-up of the trial, we consulted with Bristol Drugs Project (BDP) and its volunteer group, which included current and previous drug injectors and people with HCV infection. Members of the BDP volunteer group reviewed the invitation letter sent by practices to invite patients for an HCV test and the patient information sheet. The information resources were developed in conjunction with the Hepatitis C Trust patient group and National Hepatitis C Patient Council. The Hepatitis C Trust and BDP will also help us to co-produce a summary of the study and support dissemination of findings with patients and practitioners

Results

Practice recruitment

The NIHR South West of England Clinical Research Network invited 90 practices across Bristol, North Somerset, and Gloucestershire; 45 practices agreed, and 22 were randomised to the intervention and 23 to the control arm. Figure 1 shows the CONSORT flow diagram. The intervention and control practices were comparable in mean list size, area deprivation score, and proportion of the local community of non-white ethnicity. None of the intervention practices opted to ask new patients about injecting drug use history at registration; 15/22 practices carried out all of the other elements of the intervention (fig 1). Outcome and risk algorithm data were collected from all of the 22 intervention practices and 21/23 control practices. Two intervention practices merged during the study period, which we treat as one in our analyses.

HCV audit risk algorithm

The total number of patients identified in both control and intervention practices was 24 473—approximately 5% of the patient list, varying from 0.2% to more than

13% by practice (supplementary table S1A and S1B). Table 2 shows the frequency with which each of the risk criteria was met by the patients identified, with 8838 (36%) meeting two or more criteria. The proportion of patients identified with an opioid/injecting drug use history was approximately 1%, ranging from less than 0.1% to more than 6%. More than half of the cohort had evidence of a previous HCV test (63% in intervention and 57% in control practices). Other common criteria were a history of injecting or opioid drug use (2930 (22%) in intervention and 3315 (29%) in control practices) and unexplained elevated alanine aminotransferase concentrations.

HCV testing

Pre-intervention

At baseline, in the six month period immediately before the study period, 608/13 097 (4.6%) of the patients in the intervention practices and 380/11 376 (3.3%) of those in the control practices who were identified by the algorithm were tested for HCV. HCV testing for patients identified with opioid/injecting drug use history was 69/2930 (2.4%) and 48/3315 (1.4%) in the six months before the intervention in intervention and control practices respectively.

Post-intervention

During the study period, 2071 (16%) of patients identified in the intervention practices and 1163 (10%) of those in control practices were tested for HCV (table 3). We found strong evidence of a higher rate of antibody testing in the intervention practices (adjusted rate ratio 1.59, 95% confidence interval 1.21 to 2.08; $P < 0.001$) compared with the control practices. The magnitude of this intervention effect was unaffected by adjustment for practice location and historical HCV testing rate. We estimated the crude risk difference to be 5.6% (95% confidence interval 4.8% to 6.4%), and the adjusted estimate with variation between general practices accommodated was 5.3% (2.2% to 8.51%).

Table 1 | Unit costs (2016/17) used in economic analysis and Markov model

Item	Unit cost	Source
Cost of Audit+ (per practice)	£500 (£0 in sensitivity analysis)	Assumption
Trainer time (per hour)	£53	Estimate
Trainer travel expenses (per mile)	£0.45	University of Bristol policy
GP time (per hour)	£137	Unit costs of health and social care
Administrative staff (band 2) time (per hour)	£23	Unit costs of health and social care
Healthcare assistant (band 2)	£23	Unit costs of health and social care
Nursing staff (band 6)	£44	Unit costs of health and social care
Practice manager (band 7)	£53	Unit costs of health and social care
Phlebotomy appointment	£14.10	Based on private practice (SE Bridge Street Medical Centre)
HCV antibody blood test	£8.12	Public Health England
HCV PCR blood test	£ 90.64	Public Health England
HCV related GP consultation	£37	Unit costs of health and social care
Hepatology consultation	£219	NHS reference costs
Hepatology evaluation (outpatient, initial)	£238	NHS reference costs
Hepatology evaluation (outpatient, follow-up)	£262	NHS reference costs
DAA treatment (first treatment)	£10 000	Hurley 2018
DAA treatment (retreatment)	£15 000	Assumption
DAA treatment monitoring	£1,310	NHS reference costs

DAA=direct acting antiviral; GP=general practitioner; HCV=hepatitis C virus; PCR=polymerase chain reaction.

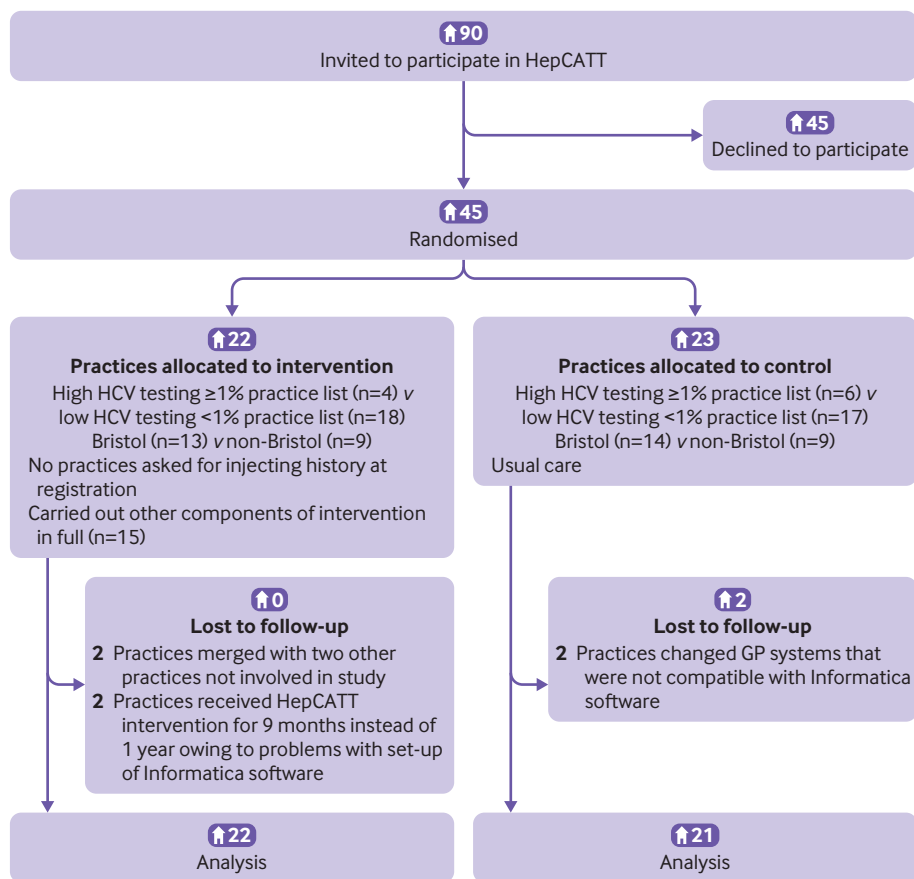


Fig 1 | Consort diagram. No practices added “have you ever injected recreational drugs?” to their patient registration proforma. Mean patients registered: intervention 11 225 (SD 4245), control 10 937 (3916); mean area deprivation score: intervention 6 (3.26), control 6 (3.23); mean % non-white ethnic population: intervention 12 (14.25), control 11 (11.49). GP=general practice; HCV=hepatitis C virus

In an exploratory analysis, also shown in table 3, we found that the intervention had a slightly greater effect on patients with an opioid/injecting drug use history (adjusted rate ratio 2.73) than other patient risk groups (adjusted rate ratio 1.45), with evidence against the null hypothesis of equal intervention rate ratios between the two subgroups (interaction test $P<0.001$). The crude risk differences, however, were similar in the two subgroups at 4–5%.

We estimate that the intra-cluster correlation coefficient was 0.067 (95% confidence interval 0.042 to 0.105) on the basis of a random effects logistic regression model (with the same covariates as the adjusted model in table 3) to allow comparison with the estimate used in the sample size calculation.

Other outcomes: HCV test yield, chronic infection, referral and assessment

The rate of positive antibody tests was also greater in the intervention practices compared with the control practices (table 3) (1.0% v 0.5%; adjusted rate ratio 2.24, 1.47 to 3.42). A greater proportion of the antibody tests were positive in the intervention group (6.4%; 129/2017) than in the control group (4.4%; 51/1163), although the evidence was weaker and consistent with chance (adjusted risk ratio 1.40, 0.99 to 1.95; $P=0.053$).

Of those people with a positive antibody test, no polymerase chain reaction tests were recorded for 9/129 patients in intervention practices and 1/51 patients in the control practices, and insufficient

Table 2 | Number of participants in intervention and control practices meeting each hepatitis C virus (HCV) audit criterion. All cohort members met one or more criteria

HCV audit criteria	Intervention (n=13 097): positive risk criteria (%)	Control (n=11 376): positive risk criteria (%)
History of HCV exposure or testing	8295 (63.3)	6476 (56.9)
History of opioid/injecting drug use	2930 (22.4)	3315 (29.1)
History of HIV or HBV infection	971 (7.4)	829 (7.3)
History of blood transfusion or transplant	423 (3.2)	378 (3.3)
History of childhood in care or imprisonment	899 (6.9)	1024 (9.0)
Altered ALT concentration	5120 (39.1)	3895 (34.2)

ALT=alanine aminotransferase; HBV=hepatitis B virus.

Table 3 | Hepatitis C virus (HCV) antibody testing, HCV positive test yield, polymerase chain reaction (PCR) tests for chronic infection, and referral to secondary care in intervention and control practices, with intervention effect estimated as rate ratio from random effects Poisson regression model that accommodates any variations in testing between practices

	Number (%)		Rate ratio (95% CI)	P value
	Intervention (n=13 097)	Control (n=11 376)		
Tested				
Crude	2071 (15.8)	1163 (10.2)	1.57 (1.18 to 2.09)	0.002
Adjusted*			1.59 (1.21 to 2.08)	<0.001
Subgroup analysis†:				
Opioid/injecting drug use	189/2930 (6.5)	80/3315 (2.4)	2.73 (1.95 to 3.82)	-
No opioid/injecting drug use	1882/10 167 (18.5)	1083/8061 (13.4)	1.45 (1.08 to 1.95)	-
Ratio of rate ratios‡	-	-	1.91 (1.45 to 2.52)	<0.001
Antibody test positive				
Crude	129 (1.0)	51 (0.4)	2.30 (1.41 to 3.75)	0.001
Adjusted*			2.24 (1.47 to 3.42)	<0.001
PCR test positive				
Crude	43 (0.3)	13 (0.1)	3.17 (1.38 to 7.31)	0.007
Adjusted*			2.96 (1.34 to 6.58)	0.008
Referred/positive antibody and PCR tests				
Crude	20 (0.2)	3 (<0.1)	6.25 (1.67 to 23.38)	0.007
Adjusted*			5.78 (1.55 to 21.61)	0.009
Referred/positive antibody test (sensitivity analysis)				
Crude	27 (0.2)	7 (<0.1)	3.43 (1.36 to 8.65)	0.009
Adjusted*			3.40 (1.35 to 8.52)	0.009

*Adjusted for practice location (Bristol versus elsewhere) and historical HCV testing rate (low versus high, as indicated by Public Health England).

†Subgroups defined by history of opioid/injecting drug use.

‡Estimated ratio of rate ratios in two subgroups (opioid/injecting drug use and no opioid/injecting drug use, and control practices as reference within each), with interaction test P value estimated from model with covariates as in above*.

sample (no result) was recorded for an additional 17 intervention and 14 control patients. Evidence of chronic disease from polymerase chain reaction tests in primary care, in people with a positive antibody test, was detected in 43 (0.3%) in intervention practices and 13 (0.1%) in control practices (table 3) (adjusted rate ratio 2.96, 1.34 to 6.58).

We found strong evidence that referral and assessment were increased in intervention practices compared with control practices (adjusted rate ratio 5.78, 1.55 to 21.6). The absolute difference between intervention and control practices, however, was modest: 20/43 patients with HCV RNA detected or 15 in 10 000 patients at high risk in intervention practices, compared with 3/13 or 3 in 10 000 patients at high risk from control practices. This equates to a number needed to help of one extra HCV diagnosis, referral, and assessment per 792 (95% confidence interval 558-1883) patients flagged. In a sensitivity analysis relaxing the requirement for a positive polymerase chain reaction test from primary care, the intervention effect was slightly attenuated but still strong (adjusted rate ratio 3.40, 1.35 to 8.52).

Change in baseline HCV testing: potential contamination/dilution of effect

Supplementary table S1A shows evidence that HCV testing increased in general in the community. Overall and in 18/21 of the control practices, the number and proportion of HCV tests among patients at high risk in the six months before the intervention (380; 3.3%) more than doubled during the intervention period (1163; 10.2%). We found no evidence that testing increased over time in control practices among patients

with an opioid/injecting drug use history (HCV testing in this patient group was 1.4% in the six months before the intervention and 2.4% in the 12 months during the intervention).

Economic evaluation

A small number of patients (287/24 473 (1.2%) appeared in the records of more than one practice. We retained these in the analysis of the intervention effect reported above to avoid excluding a more mobile section of the study sample but excluded them from the economic analysis, which is based on the remaining 23 896 patients (12 922 in the intervention arm and 10 974 in the control arm).

High variability existed between practices in the time estimated to complete each stage of the case finding process (supplementary table S2). The most time consuming stage was screening the list of patients to identify appropriate candidates for the screening invitation; this varied from an estimated one hour to 30 hours. This stage was also the most expensive, as the task was most often carried out by a general practitioner. Other elements of the case finding were more often carried out by the practice manager or administrative staff. The mean total cost of the case finding process was £1272 per practice, or £624 per practice if software and installation costs are excluded.

The intervention led to a very small increase in the number and the cost of HCV related general practice consultations during the study period, but this had little effect on total costs (table 4). The additional cost of case finding per patient at risk in the intervention practices was £7.10 (95% confidence interval £4.75 to £9.45). The average cost per additional patient

Table 4 | Cost effectiveness of hepatitis C virus (HCV) case finding

Task	Intervention (n=12 922)	Control (n=10 974)	Difference (95% CI)
Training cost	£1.22	£0	-
Screening cost	£2.06	£0	-
Mean HCV antibody test cost per patient	£3.54	£2.33	£1.21 (£1.02 to £1.40)
Mean HCV PCR test cost per patient	£0.89	£0.41	£0.48 (£0.28 to £0.68)
No (%) HCV related consultations: no; yes	12 187 (94); 735 (6)	10 467 (95); 507 (5)	
Mean HCV related consultation cost per patient	£2.27	£2.10	£0.17 (-£0.09 to £0.44)
Mean hepatology referral cost per patient	£0.44	£0.12	£0.32 (£0.12 to £0.52)
Total mean case finding cost per patient	£10.42	£4.96	£7.10 (£4.75 to £9.45)*
No (%) patients referred to hepatology for treatment	20 (0.15)	3 (0.03)	-
Cost per additional patient referred to hepatology for treatment	-	-	£5569

PCR=polymerase chain reaction.

*Adjusted mean difference from mixed effects linear regression, clustered by practice, adjusted for previous HCV testing, Bristol practice, and length of follow-up.

referred to hepatology for assessment was £5569. Figure 2 shows the cost effectiveness acceptability curve based on the cost per additional case identified. Alternatively, after exclusion of the training, software, and installation costs, the cost of case finding was £4.03 (£2.27 to £5.80) and the average cost per additional patient referred to hepatology for treatment was £3165.

Economic model

Table 5 shows the estimated ICERs per QALY gained from the economic model. The base case analysis generated an ICER of £7431 per QALY with a probability of 89.7% of being below £20 000 per QALY (fig 3). After exclusion of training and installation costs, the ICER was £6212 per QALY (with 92.5% probability of being below £20 000 per QALY). Table 5 also shows our sensitivity analyses. The intervention was still cost effective when we assumed no effect of the intervention on the linkage to care (ICER £19 653 per QALY) and a reduced utility in patients who may continue to be opioid dependent and/or inject drugs (ICER £9093 per QALY) and was more cost effective when we assumed lower HCV drug costs (ICER £5641 per QALY).

Threshold analyses

In our threshold analysis of the effect of the intervention on the rate ratio of antibody testing, the base case analysis will always be cost effective at an ICER less than £20 000 per QALY because the intervention led to

higher linkage to care. If we assume that linkage to care was equal for control and intervention practices, then the cost effectiveness threshold for the intervention effect of increasing HCV antibody testing was a rate ratio of 1.56 (or a 56% increase in HCV testing).

Discussion

The size of the effect of the HepCATT primary care intervention was comparatively modest but at low cost to the NHS. The risk difference was 1.3 per 1000 or a “number needed to help” of one extra HCV diagnosis, referral, and assessment per 792 patients flagged on primary care systems. A threefold to sixfold increase in linkage to specialist care occurred. The intervention cost was £624 per practice (with software and installation costs removed as the HCV audit tool is now incorporated in many clinical software systems) equating to approximately £4.03 per patient flagged, an average cost per additional patient referred to HCV specialist services of £3165 and an ICER of £6212 per QALY (well below NICE’s guidance of £20 000 per QALY or even the average cost of NHS treatments of approximately £13 000 per QALY²⁵).

Limitations of study

Overall, the trial was completed as planned, but some potential limitations to the study exist. Firstly, we detected some evidence of contamination between control and intervention sites. A clear increase in HCV testing during the intervention period occurred among people with a previous HCV test in the control practices, but we found no evidence of any increase in testing in those with an opioid/injecting drug use history. This was probably due to increased steps nationally and regionally to increase HCV testing as part of HCV treatment targets for operational delivery networks. Nevertheless, the HepCATT intervention managed to increase uptake of HCV testing and increased linkage to care.

Secondly, our sample size calculations had assumed that around 10 people at high risk would be identified per practice and that we would have sufficient power to detect a difference in HCV testing between 5% in the control group to 17% in the intervention group. In our trial, the average number of patients flagged (across control and intervention practices) was more than

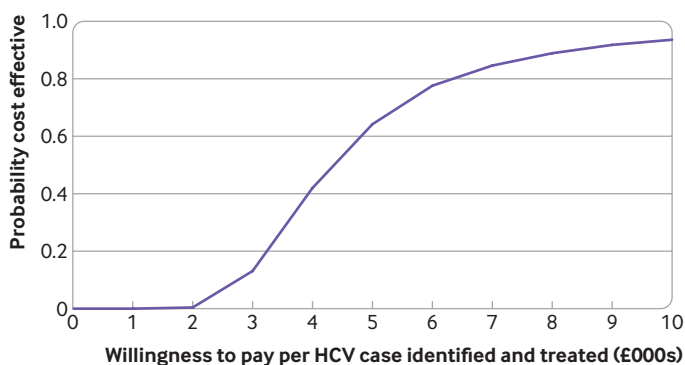


Fig 2 | Probability that hepatitis C virus (HCV) case finding is cost effective per additional case identified: cost effectiveness acceptability curve

Testing option	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Base case results:					
Control arm	£409	16.2202	-	-	-
Intervention arm	£416	16.2212	£7.44	0.00100	£7431
Training costs excluded:					
Control arm	£409	16.2202	-	-	-
Intervention arm	£415	16.2212	£6.22	0.00100	£6212
Scenario—no treatment effect for linkage to care (referral and attendance):					
Control arm	£408	16.2206	-	-	-
Intervention arm	£417	16.2210	£8.44	0.00043	£19 653
Scenario: £5000 per DAA:					
Control arm	£382	16.2202	-	-	-
Intervention arm	£388	16.2212	£5.64	0.00100	£5641
Scenario—utility adjusted to PWID utilities (all multiplied by 0.82):					
Control arm	£409	13.2552	-	-	-
Intervention arm	£416	13.2561	£7.44	0.00082	£9093

DAA=direct acting antiviral; ICER=incremental cost effectiveness ratio; PWID=people who inject drugs; QALY=quality adjusted life year.

500 and the average number of people with an opioid/injecting drug use history was 148. The observed difference was smaller than anticipated, partly because of improvements in HCV testing in the community, and the intra-cluster correlation coefficient at 0.067 was marginally greater than our assumed 0.05, but both of these factors will have been more than offset by the greater than anticipated number of people at high risk found at the vast majority of practices.

Thirdly, as this was a cluster randomised controlled trial, we did not seek consent from individual patients for participation in the full study (which was justified as the intervention was following NICE recommendations). A consequence of this was that we did not seek patients' consent to examine their records—for example, to explore reasons for the insufficient samples for polymerase chain reaction testing in so many cases.

Fourthly, general population samples tend to find a lower proportion of people with chronic disease (detectable HCV RNA/ polymerase chain reaction positive) than do clinical samples.^{26 27} In our sample—excluding those with no polymerase chain reaction tests or tests with insufficient sample—we found that 40% had chronic HCV infection. It was not clear whether this was because people had been previously

treated (but not recorded in clinical information that could be searched by the HCV algorithm) or had cleared the virus and previously been found to be HCV negative. This reduces the yield and potentially the cost effectiveness of the intervention (although the intervention was shown to be highly cost effective).

Other evidence

Large scale trials on HCV case finding in primary care are rare.¹³ We also did a pilot trial of NICE recommendations to appoint HCV case facilitators in community drug clinics.²⁸ The original cost effectiveness model underpinning NICE guidance in primary care was based on a non-randomised pilot study in eight practices with high levels of deprivation.¹⁴ The earlier study used financial incentives for participation, searched practice lists for a smaller sub-group of patients with a history of opioid dependence, and the intervention was estimated to be less cost effective than ours (at an estimated ICER of £13 900 per QALY), although the original pilot generated a higher yield of patients with chronic HCV infection.

A recent complementary trial (HepFREE), also motivated by the lack of robust evidence in support of NICE guidance on hepatitis case finding,^{17 19} showed that combining case finding for HCV and hepatitis B virus in migrant populations in primary care could be effective and broadly cost effective.²⁹ The HepFREE trial was conducted in general practices with a high density of migrants and involved a modest incentive (£500) for general practitioners to run an algorithm that would identify patients for contacting by letter and add an electronic prompt to the patient's record. Additional clinical support was available to help practices run the case finding exercise. HepFREE also found a comparatively low proportion of viraemic patients (at approximately a third of people with HCV antibody tests), which as for HepCATT reduces the yield of the study and has implications for the re-engagement exercise recently launched by Public Health England and NHS England (<https://www.gov>

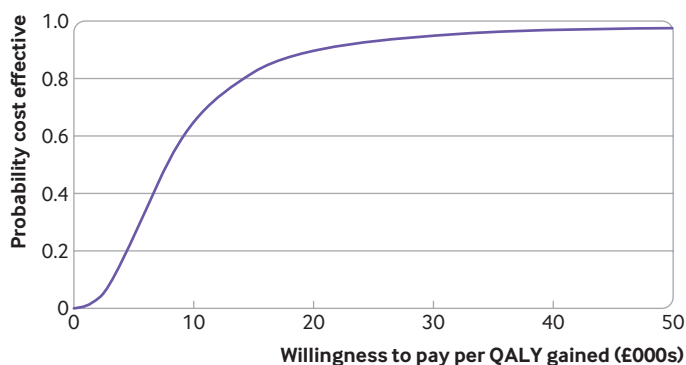


Fig 3 | Probabilistic sensitivity analysis that hepatitis C virus case finding is cost effective at different thresholds of willingness to pay per quality adjusted life year (QALY)

uk/government/publications/hepatitis-c-patient-re-engagement-exercise).

A previous study in Ireland found an increase in HCV testing in general practices that were encouraged to follow clinical guidelines recommending HCV testing for patients taking methadone.³⁰ In the UK, case finding and early treatment for opioid dependent patients has been established to be highly cost effective, and multiple alternative case finding and care pathways are being tested and developed in the community for this population group, including through prisons, pharmacies, needle exchange services, and homeless services.^{12 28 31 32} However, these care pathways do not cover our study patients—people in primary care who may no longer be opioid dependent or taking opioid agonist treatment.

An alternative, and possibly complementary, approach is to conduct birth cohort screening, whereby all patients born between specific years (such as 1945 to 1965 as recommended by the Centers for Disease Control and Prevention in the US) are invited to be screened for HCV.^{33 34} An economic model suggests that adding HCV screening to the NHS health check for people aged 45 to 70 could be cost effective, although no empirical evidence yet supports such a change³⁵

Implications

The nested qualitative study suggests that practices are willing to engage with our intervention.¹⁶ Our intervention was highly cost effective but increased HCV testing by only a modest amount—lower than expected from our original sample size calculation. The overall findings are strong enough for us to recommend optimisation as part of implementation across primary care in the UK. However, HepCATT cannot be seen as the only solution to increasing HCV case finding in primary care and to identifying patients at risk who may not be aware of their HCV infection. Other interventions, such as evaluating birth cohort screening as part of NHS health checks, and additional components to the HepCATT intervention, such as incentives for the practices for running the algorithm and additional clinical support for achieving higher uptake, are needed to enhance the impact.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: support for the submitted work as described above; MH has received unrestricted honorariums for presenting at meetings from Abbvie, Gilead, and MSD; PV has received unrestricted honorariums for presenting at meetings from Abbvie and Gilead; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This trial was approved by the South West Frenchay Research Ethics Committee and carried out in accordance to the declaration of Helsinki and all UK regulatory requirements.

Data sharing: The algorithm is defined in the supplementary materials, and the software is now available for practices and the NHS. Relevant anonymised data will be made available on reasonable request.

Transparency declaration: The lead author and guarantor affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

Dissemination to participants and related patient and public communities: The authors plan to send a summary of the results to participating practices and undertake extensive knowledge exchange work with the NHS (primary care, Public Health England, HCV operational delivery networks, NHS England, and public health departments in local government). They will co-produce summary information on the study with Bristol Drug Project and Hepatitis C Trust.

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Supplementary materials