a) Title

Effectiveness of interventions to increase hepatitis C testing uptake among high-risk groups: a systematic review

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ABSTRACT

Background: People who inject drugs are at the greatest risk of acquiring hepatitis C virus infection in many high income countries, including those in Europe. Our review examined the effectiveness of interventions aimed at increasing hepatitis C virus testing uptake.

Methods: We undertook a systematic review of controlled studies. Searches of 13 databases were supplemented with citation searching, and manual searches of reference lists and websites. Studies of interventions that aimed to increase testing uptake among high-risk groups were included. Testing uptake was our primary outcome measure of interest and secondary outcomes were engagement in follow-up services or treatment. A narrative synthesis was undertaken.

Results: Eight controlled studies were included. Three studies examined interventions in primary care; one examined dry blood spot testing as an alternative method of testing, and two examined outreach provision. Two further studies examined interventions to improve hepatitis C management. Targeted case finding in primary care, support and training for primary care practitioners, offering alternative testing, and provision of outreach testing all increased uptake of testing; however intervention effects were variable.

Conclusions: Evidence from the available studies suggests that increases in testing uptake can be achieved. Careful attention needs to be paid to the resource implications associated with implementation of interventions in primary care settings and also of the potential for interventions to improve outcomes once a positive diagnosis has been made. Further research on the cost-effectiveness of the intervention approaches examined in this review is required.

Keywords: Hepatitis C; Intervention Studies; Substance Abuse, Intravenous

INTRODUCTION

Hepatitis C virus infection represents a major public health problem worldwide.[1] Within the World Health Organization (WHO) European region, approximately nine million people are chronically infected with the hepatitis C virus (HCV),[2] and as in other high-income regions, people who inject drugs (PWIDs) are at greatest risk of acquiring infection.[3] Despite the burden associated with HCV, it is still a neglected disease in many countries in Europe.[4] A Call to Action for the EU and Member States on hepatitis B and C was launched in 2011 with the goal of making viral hepatitis a public health priority.[5] Within the last decade, calls for action have also been launched in individual European countries, but with differing levels of success.[6] So far, government-led, sustainable improvements in screening of high-risk groups have only been made in France and Scotland.[4] Whilst effective antiviral therapies for HCV have become available within the last decade, coordinated and robust responses to the broader public health issues associated with tackling transmission of the virus have lagged behind.[5 7] In many European countries, problems persist in the effective diagnosis and referral of patients and although knowledge of HCV status is critical for preventing transmission and for initiating early treatment and care, the European Liver Patients Association found that many people are unaware of their HCV status at the time of infection.[7] Furthermore, although an increasing number of studies have shown that PWIDs who have acquired HCV can be successfully treated,[9 10] very few go on to receive HCV treatment.[11-13]

European countries are therefore facing a major challenge to improve identification of individuals at high-risk of HCV. In order to inform policy and practice responses, we carried out a systematic review of the effectiveness of interventions aimed at increasing uptake of case finding and testing among high-risk groups and health professionals involved in the promotion or provision of HCV testing.

METHODS

This study was conducted as part of a series of extensive systematic reviews to inform policy recommendations on ways of offering hepatitis B (HBV) and HCV testing in England by the National Institute for Health and Clinical Excellence (NICE). We conducted our systematic review in accordance with NICE methods[14] and followed the PRISMA statement for transparent reporting. Accordingly, a protocol documenting the background, objectives and methods was prepared in advance of the review (available on request from the authors).

Search strategy

A comprehensive search approach was taken. Searches were conducted in 13 databases (see Figure 1), with additionally, citation searching, searches of the reference lists of retrieved studies and searches of relevant websites. Searches were limited to articles published since 1990 and were conducted in July 2011.

Search strategies were developed for each database using a combination of free text and thesaurus terms. As this work was conducted as part of a broader review on HBV and HCV testing search terms relating to both types of hepatitis (e.g. by exploding the MeSH term 'Hepatitis C') and testing (e.g. case find*, test*) were combined with relevant terms for intervention, outcome and evaluation, professional role, setting, population or professional education.

Study selection and eligibility criteria

Titles and abstracts were initially screened by one reviewer from a team of three (LJ, EMC and GB) and the lead reviewer (LJ) independently second screened 30% of the references. Titles and abstracts of any potentially relevant articles identified at this stage were then rescreened by two reviewers from the same team. Relevant articles identified following this

stage were retrieved as full text publications and screened by two reviewers independently (again from the same team) to determine whether the study met the inclusion criteria. While studies of any design were eligible for inclusion in the broader review for this paper we focused on the findings from controlled studies, further limiting inclusion to randomised controlled trials (RCTs), controlled non-randomised studies (NRCTs), and controlled before and after (CBA) studies that compared an intervention against no intervention or another type of intervention (e.g. continuation of current testing practice). Fourteen uncontrolled studies (e.g. case series) were identified through our searches, but were excluded from the main analyses presented here. We included studies of any type of intervention that aimed to raise awareness of, or engagement in, HCV testing among high-risk groups. HCV infection is highly prevalent among PWID and while they are the population primarily targeted for HCV testing studies of interventions that targeted non-PWID high-risk populations were also included. Studies that focused on changing behaviours in relation to injection or sharing practices among PWIDs, but without reference to HCV testing, were not eligible for inclusion. Change in testing uptake was the primary outcome measure of interest. We defined this broadly, including changes in the number of participants: (i) requesting or accepting a test; (ii) undergoing testing; (iii) receiving a positive test; or (iv) referred to treatment. Changes in the number of participants testing positive who engaged in follow-up services and/or treatment were examined as secondary outcomes.

Data extraction and quality assessment

Data relating to study design and quality were extracted by one reviewer from a team of two (EMC and GB) and independently checked for accuracy by a second reviewer (LJ). Disagreements were resolved through consensus and when necessary a third reviewer consulted. Data were extracted from the included studies on: author; publication year; country; research funding source; study objectives; study design/characteristics (e.g.

eligibility criteria); participants (e.g. age and gender); intervention; analysis/outcomes measured; and results. Two reviewers independently undertook quality assessment using NICE checklist criteria;[14] a revised version of the Graphical Appraisal Tool for Epidemiological studies.[15]

Data analysis and synthesis

We summarised the outcomes of data extraction and quality assessment in tables and as a narrative summary. Studies were grouped according to the type of intervention examined and the possible effects of study quality on the effectiveness data and review findings discussed. Where possible, intervention effectiveness was investigated by examining the difference between pre- and post-intervention changes in testing uptake. Otherwise, effectiveness was investigated by examining the difference in post-intervention testing uptake between intervention and control groups. To provide a comparison of effect sizes across the interventions examined we used Wilson's Effect Size Calculator[16] to calculate Cohen's *d* and corresponding 95% confidence intervals using the logit method based on the proportion of intervention and control participants completing a HCV test. We chose not to pool effect sizes due to heterogeneity across the studies in the populations, settings and interventions examined. We developed a logic model to guide the narrative synthesis and to explore potential relationships between the interventions identified and outcomes. The logic model (Figure 2) depicts the links between the types of interventions identified, the settings in which they are delivered and the intended change in outcomes.

RESULTS

We retrieved 12,656 references and assessed 299 full text articles (Figure 1). Eight controlled studies, from the UK,[17-19] France,[20 21] the Netherlands,[22] Ireland,[23] and the USA[24] met our inclusion criteria (Table 1). This included five RCT and three NRCTs. Three studies

examined interventions designed to enhance case finding and testing in primary care.[17 18 20] One study examined interventions designed to increase access to testing services based on offering alternative methods of testing,[19] and two studies[21 24] examined HCV testing in outreach settings. Two studies[22 23] examined interventions designed to improve management of HCV among health professionals.

Raising awareness and encouraging use of testing services

A French study[20] examined the impact of assistance with HCV screening for general practitioners (GPs). GPs receiving the intervention were assisted with the screening programme through the provision of information (posters/leaflets) in surgery waiting rooms. Two UK studies[17 18] evaluated opportunistic case finding in general practices in areas of high injecting drug use and HCV prevalence. Both interventions targeted individuals aged 30-54 years, and the intervention examined by Cullen and colleagues[18] was also limited to individuals with indicators of past injecting drug use. All patients meeting the inclusion criteria and attending for non-urgent appointments were offered screening and given an information leaflet; individuals accepting the offer could immediately attend, or return for, an appointment.

In the French study,[20] provision of patient information was associated with a significantly higher number of post-intervention patient requests for testing compared with GPs receiving training only. HCV tests were undertaken at the request of the patient in 35.7% of cases in intervention practices compared to 19.5% of cases in control practices ($p<0.001$ for comparison).[20] However, although this demonstrated the value of providing information to patients, there was no significant impact on the overall number of tests requested per GP in intervention and control practices (net difference in post-intervention tests requested per GP = -0.5 tests). Two UK studies[17 18] found that targeted case finding in primary care had a positive

impact on the number of patients offered and accepting a test. In one study,[17] the proportion of eligible patients tested increased from pre- to post-intervention by 9.9% in the intervention practice compared to a decrease of 0.1% in the control practice. Intervention was associated with low diagnostic yield, with 12.8% of intervention patients (n=15/117) testing HCV positive. No control patients were tested during the intervention period.[17] Among intervention practices that implemented a case finding intervention specifically targeting former PWIDs, 0.8% of the practice population aged 30-54 years were tested for HCV compared to 0.3% in control practices.[18] The proportion of patients who were tested and received a positive (antibody) test was 70.5% in intervention practices compared to 22.2% in control practices.

Opportunistic case finding in primary care was found to have had a mixed impact on the number of patients starting HCV treatment following referral.[17 18] Although referral rates were relatively high (Table 2), both studies found a high rate of failure to attend, and dropout from, follow-up services (around 70%[17] and 50%[18] in the two studies, respectively). Neither study examined reasons for non-attendance or dropout.

Increasing access to testing services

One cluster RCT[19] examined the impact of offering dried blood spot (DBS) testing as an alternative to venepuncture in substance misuse services, drug clinics and prisons. Hickman and colleagues[19] randomised services to offer DBS testing undertaken by drugs workers or testing as usual. The internal validity of the study was potentially affected by inconsistency in exposure to the intervention and the authors questioned whether the study was adequately powered to detect an intervention effect. Two RCTs, based on individual[21] and cluster[24] randomisation respectively, examined whether provision of testing in non-specialist community services increased access to testing and follow-up services. One study examined an intervention targeting refugees and asylum seekers housed in shelters[24] and the other,

patients at mental health treatment sites with co-occurring mental health and substance abuse disorders.[21]

Increases in HCV testing uptake were found in drug services and prisons offering DBS testing alongside other means of testing, compared to services offering venepuncture only.[19] An overall significant positive effect of introducing DBS testing was found when all intervention sites were compared to control sites (weighted absolute increase in testing uptake = 10.8%; 95% CI: 0.1%–21%; p=0.05). However, the size of the treatment effect varied considerably across paired intervention and control sites, with differences in the proportion of patients tested ranging from -0.5% to 69.4%. Whilst reasons for variation in the treatment effect were not clear, the authors noted that the two sites with the highest difference in treatment effect attributed the increase "simply to an interest in HCV".[19]

Integration of testing services within non-specialist community settings also had a positive effect on testing uptake. Participation in the STIRR programme[21] within mental health treatment sites was associated with significantly higher acceptance of HCV testing among patients compared to control sites, in which patients were directed to off-site services (STIRR, 86.4% *vs.* control, 14.5%; p<0.001). Outreach testing,[24] also improved testing acceptance and uptake; with testing completion significantly higher among participants who received either intervention approach compared to control (on-site testing *vs*. control group: odds ratio [OR] 98.5, 95% CI 51.9–200.8; testing by referral *vs*. control group: OR 49.8, 95% CI 26.1–102.1; provision of on-site testing *vs.* testing by referral OR 2.0, 95% CI: 1.3–2.9). However, despite the positive intervention effects, 30% of participants accepting a test did not complete one, with the authors finding that participants changed their minds because of a fear of having blood taken.

Aimed at professionals

Two studies[22] [23] examined interventions designed to improve health professionals' management of HCV testing and treatment. Both studies[22] [23] evaluated complex interventions, comprising educational materials and education sessions for GPs in support of a public awareness campaign[22] in a NRCT, and a nurse-led 6-month intervention to support the implementation of guidelines on the management of HCV in primary care in an cluster RCT.[23]

The intervention supporting implementation of clinical guidelines improved HCV screening rates amongst patients on methadone maintenance treatment. In intervention practices, 49.0% of patients were screened compared to 27.2% of the control group (adjusted OR: 3.76, 95% CI 1.3–11.3).[23] Educational materials and education sessions for primary care practices also had positive intervention effects on testing uptake.[22] The post-intervention testing uptake in the intervention region was 2.2 times (95% CI 1.5–3.3) as high as in the control region and the intervention was associated with a 2.6% (95% CI -0.7%–5.8%) increase in the number of positive tests. However, the clinical significance of these comparisons was not clear and the intervention was associated with a low diagnostic yield.

Effects on referral and treatment outcomes were explored in one study.[23] The intervention supporting clinical guideline implementation was associated with an increase in referrals for assessment at a hepatology clinic. However, after correction for clustering the corresponding adjusted OR was no longer statistically significant (OR 3.15; 95% CI 0.9–10.7). The authors suggest that this finding may be explained by the short duration of the study or by this outcome being subject to a clustering effect.

Comparison of effect sizes across studies

Data was available to calculate effect sizes for six of the eight studies included in the review (Table 2). The effect sizes (Cohen's *d*) calculated ranged from 0.54 to 2.52. The largest effect

sizes were associated with interventions based on the delivery of services in non-specialist community settings.[21 24]

DISCUSSION

Main findings

We conducted a systematic review of all available controlled studies of interventions aimed at increasing uptake of voluntary HCV testing among high-risk groups. Although we found relatively few controlled studies, a range of approaches were examined, including interventions designed to enhance case finding and testing uptake in primary care,[17 18 20] offer alternative methods of testing,[19] deliver services in non-specialist community settings[21 24] and improve HCV management among health professionals.[22 23]

Based on current evidence it appears that targeted case finding, support and training for primary care practitioners, offering DBS testing, and the provision of outreach testing may increase HCV testing uptake among high-risk groups. However, the effects of these interventions on testing uptake were variable, as shown by the comparison of effect sizes. It is also important to consider the limitations of the interventions examined for improving outcomes once a positive HCV diagnosis has been made. Although this review focused primarily on testing uptake, as the primary aim of testing should be to identify positive individuals and to offer them appropriate management and treatment, it is important to note that high-risk groups, and in particular PWIDs, may encounter further barriers to care after diagnosis. These include problems with accessing referral and counselling,[25] poor attendance at follow-up services,[26 27] being denied opportunities to access treatment and receiving a lack of information on treatment options.[26 28] Further research on how to increase engagement in HCV care and treatment following a positive diagnosis is needed to ensure that such barriers are reduced. Furthermore, there needs to be a greater awareness of the potential for treatment

to substantially reduce the prevalence of HCV infection, particularly among PWIDs.[29] Primary care services are an important setting for identification of HCV infection and five of the included studies examined intervention approaches in this setting.[17 18 20 22 23] Targeted case finding increased testing uptake and case yield in general practices in areas of high HCV prevalence[16 17] but in other studies increases in diagnostic yield were low.[22] Although a cost-utility study[30 31] found it was likely that case finding for HCV in primary care among one of the key high-risk groups, in this case former users of injecting drugs, would be considered cost-effective, there were substantial uncertainties in the estimates used. The authors of two UK studies[17 18] noted that GPs had found the process of offering a test and obtaining a sample time consuming, and that sometimes multiple appointments were required to complete the testing process. The time and resource implications associated with primary care-based interventions therefore need to be considered and further research on the cost-effectiveness of this and the other intervention approaches examined in this review is required.

Uncontrolled studies

We identified six uncontrolled studies through our searches that examined intervention approaches of relevance to our review. Although the results of uncontrolled studies should be treated with great caution, they provide some further context to the intervention approaches examined in controlled studies. The potential to improve testing uptake by broadening access to HCV services within community settings was shown in four studies.[32-35] Two studies of particular relevance found that targeting current drug users through multidisciplinary or shared care approaches to HCV testing and treatment was associated with good uptake of follow-up services, and treatment outcomes considered comparable to those seen in non-drug using populations.[34 35] Drawing on qualitative research undertaken with PWIDs, convenient and opportunistic testing and location of HCV services, including treatment, in one setting appears to be an important facilitator of testing and management.[27 36] For interventions aimed

at improving professional practices, a study of a French national awareness campaign demonstrated that without support, offers of testing by primary care professionals may increase but not within the desired high-risk groups.[37] Another study[38] found that the number of clients tested for HCV was nearly six times greater after DBS testing was introduced compared to the number tested off-site by venepuncture in the previous year. The authors noted that the increase in uptake may have been attributable to the increased availability of on-site testing rather than solely to the introduction of an alternative method of testing.

Scope and limitations of the review and published literature

The scope of the review was broad and covered a range of intervention approaches and settings. The search strategy developed was comprehensive but resulted in the retrieval of a large number of irrelevant references indicating high sensitivity, but low precision. It is possible that some relevant studies were missed, but including multiple strategies minimised this likelihood. Although limiting inclusion to controlled studies excluded a number of studies of relevant approaches, including uncontrolled studies in the main analyses would have introduced the potential for bias in determining effectiveness and risked overestimation of intervention effects. Alongside this consideration, there were uncertainties as to whether potential sources of bias had been minimised in the included controlled studies. Limitations were identified using the checklist quality criteria; in three RCTs,[20 21 24] there were reservations about whether selection bias had been minimised and across all studies follow-up times were generally six months or less and consequently not long enough to fully assess the long-term harms or benefits of intervention. The internal validity of one RCT was also potentially affected by whether the study was adequately powered to detect an intervention effect.[19] In addition, effect size estimates were not reported or calculable for two studies based on non-random allocation.[17 18] A further limitation of the published literature was the differences in the types of outcomes reported across the included studies. Whilst all studies

reported a measure of the number of participants completing testing, only three studies reported the proportion of participants testing HCV positive (Table 1).

Conclusions

In conclusion, despite a number of methodological limitations, evidence from available studies of interventions aimed at increasing uptake of HCV testing with high-risk groups suggests that increases can be achieved. However, careful attention should be paid to the resource implications associated with implementation of the interventions examined in this review and of the potential for interventions to improve outcomes once a positive HCV diagnosis has been made.

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Conflicts of interest: All the authors declare that they have none.

KEYPOINTS

- Existing evidence on the effectiveness of interventions aimed at increasing engagement in testing among groups at risk of HCV infection, and health professionals involved in the promotion or provision of testing is limited.
- Eight controlled studies were identified that examined a range of approaches aimed at increasing engagement in HCV testing among high-risk populations.
- Our review indicates that targeted case finding in primary care, support and training for primary care practitioners, offering dried blood spot testing, and the provision of outreach

testing may increase uptake of HCV testing among high-risk groups; however the effects of these interventions is variable.

- The interventions examined had a limited impact of on referral and treatment outcomes following a positive HCV diagnosis.

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Table 1. Summary of study characteristics

Study	Study design	Target population (Number of patients in intervention/ control)	Setting, (Number in intervention/ control)	Intervention	Intervention phase	Outcomes								
						Requesting or accepting a test			Completing testing			HCV positive (antibody) test		
						I	C		I	C		I	C	
Anderson 2009	NRCT	Practice population aged 30-54 years (n=1,165/914)	General practices (n=1/1)	Opportunistic age criterion based screening	Before	…	…	…	0.06%	0.04%	10.0 %	…	…	
					During	…	…	…	10.0%	0.0%		12.8%	0.0%	12.8%
Cullen 2006	RCT	Health professionals (n=104/92)	General practices (n=13/12)	Implementation of clinical guidelines	Before	…	…	…	33.7%	26.1%	14.2 %	…	…	…
					During	…	…	…	49.0%	27.2%				
Cullen 2011	NRCT	Former PWIDs (n=13,037[a]/14,189)	General practices (n=8/8)	Targeted, age based screening	During	0.9%	…	…	0.8%	0.3%	0.5%	70.5%	22.2%	48.3%
Helsper 2010	NRCT	Health professionals (NR)	Primary care services (n=110/109)	Support programme	Before	…	…	…	57[b]	86[b]	…	0.0%	1.7%	2.6%
					During	…	…	…	172[b]	118[b]		1.7%	0.8%	
Hickman	RCT	PWIDs	Drug treatment	DBS testing	Before	…	…	…	8.4%	7.7%	14.5	…	…	…

Study	Study design	Target population (Number of patients in intervention/	Setting, (Number in intervention/	Intervention	Intervention phase	Outcomes								
						Requesting or accepting a test			Completing testing			HCV positive (antibody) test		
2008		(n=6,650/5,800)	clinics and prisons (n=14/14)		During	…	…	…	20.6%	5.4%	%			
Rosenberg 2010	RCT	Co-occurring mental health/substance use disorders (n=118/118)	Mental health programme (NR)	Direct provision of BBV services	Before	…	…	…	18.6%	22.9%	76.2 %	…	…	…
					During	…	…	…	86.4%	14.5%				
Roudot-Thorval 2000	RCT	GPs	General practices (n=94/90)	Posters and leaflets in waiting room	During	35.7%	19.5%	7.0%	3.1[c]	3.6[c]				
Sahajian 2011	RCT	Refugees and asylum seekers (n= A 222; B 243/811)	Homeless shelters (n=A 6; B 6/6)	A Testing by referral	During	72.5%	NR	NR	42.8%	1.5%	41.3 %	NR	NR	…
				B On-site testing	During	77.4%	NR	NR	59.7%	1.5%	58.2 %			

BBV, blood borne virus; C, control group; DBS, dry blood spot; GP, general practitioner; I, intervention group; NRCT, non-randomised controlled trial; PWID, people who inject drugs. RCT,

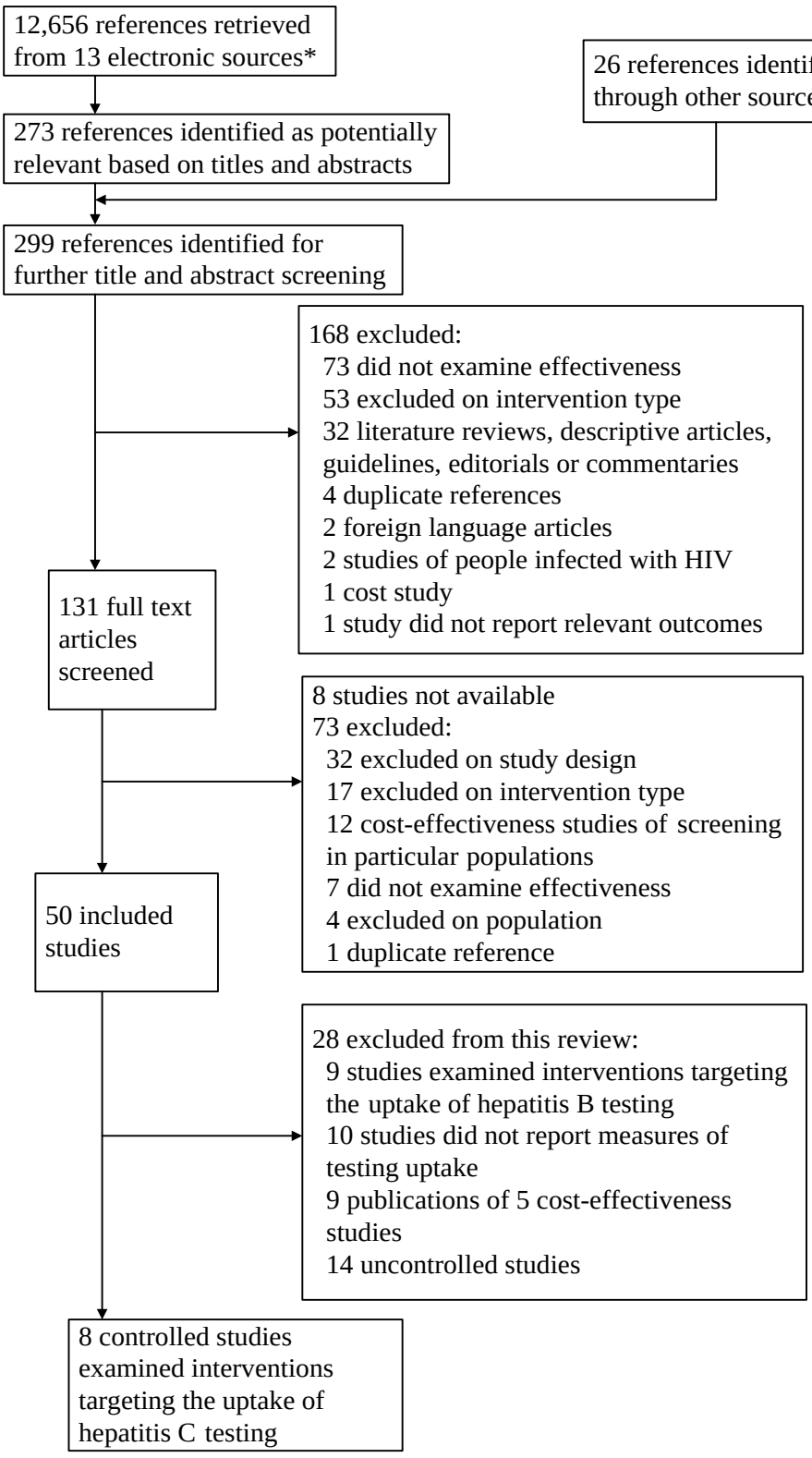
Study	Study design	Target population (Number of patients in intervention/	Setting, (Number in intervention/	Intervention	Interventio n phase	Outcomes		
						Requesting or accepting a test	Completing testing	HCV positive (antibody) test

randomised controlled trial; NR, not reported; ⋯, outcome not reported; [a]Based on practice population aged 30-54 years (n=485 with a history of injecting drug use); [b] Number of tests. [c] Number of tests per GP

Table 2. Comparison of effect sizes across the included studies

Study	Sample size		Proportion completing test		Pre and post difference %		Effect size (95% CI)
	I	C	I %	C %	Ipost-Ipre	Cpost-Cpre	
Anderson 2009	1,165	914	10.0	0.0	9.9	-0.1	Not calculable
Cullen 2006	104	92	49.0	27.2	15.4	1.1	1.54 (0.42, 2.66)
Cullen 2011	13,037	14189	0.8	0.3	0.8	0.3	0.54 (0.35, 0.74)
Helsper 2010	NR	NR	⋯	⋯			Not calculable
Hickman 2008	6,650	5800	20.6	5.4	12.2	-2.3	0.84 (0.76, 0.91) [a]
Rosenberg 2010	81	69	86.4	14.5	67.8	-8.4	2.00 (1.49, 2.51) [a]
Roudot-Thorval 2000	NR	NR	⋯	⋯			Not calculable
Sahajian 2011; Testing by referral	222	811	42.8	1.5	42.8	1.5	2.15 (1.80, 2.49)
Sahajian 2011; On-site testing	243	811	59.7	1.5	59.7	1.5	2.52 (2.18, 2.87)

NR, not reported; ⋯, outcome not reported; [a] Calculated based on post intervention difference.



*ASSIA, the British Nursing Index, CINAHL, The Cochrane Library, EMBASE, the EPPI Centre databases, the British Library Electronic Theses Online Service, King's Fund catalogue, MEDLINE, PsycINFO, Social Care Online, Social Science Citation Index and Sociological Abstracts

Figure 2. Flow of information through the different phases of the systematic review

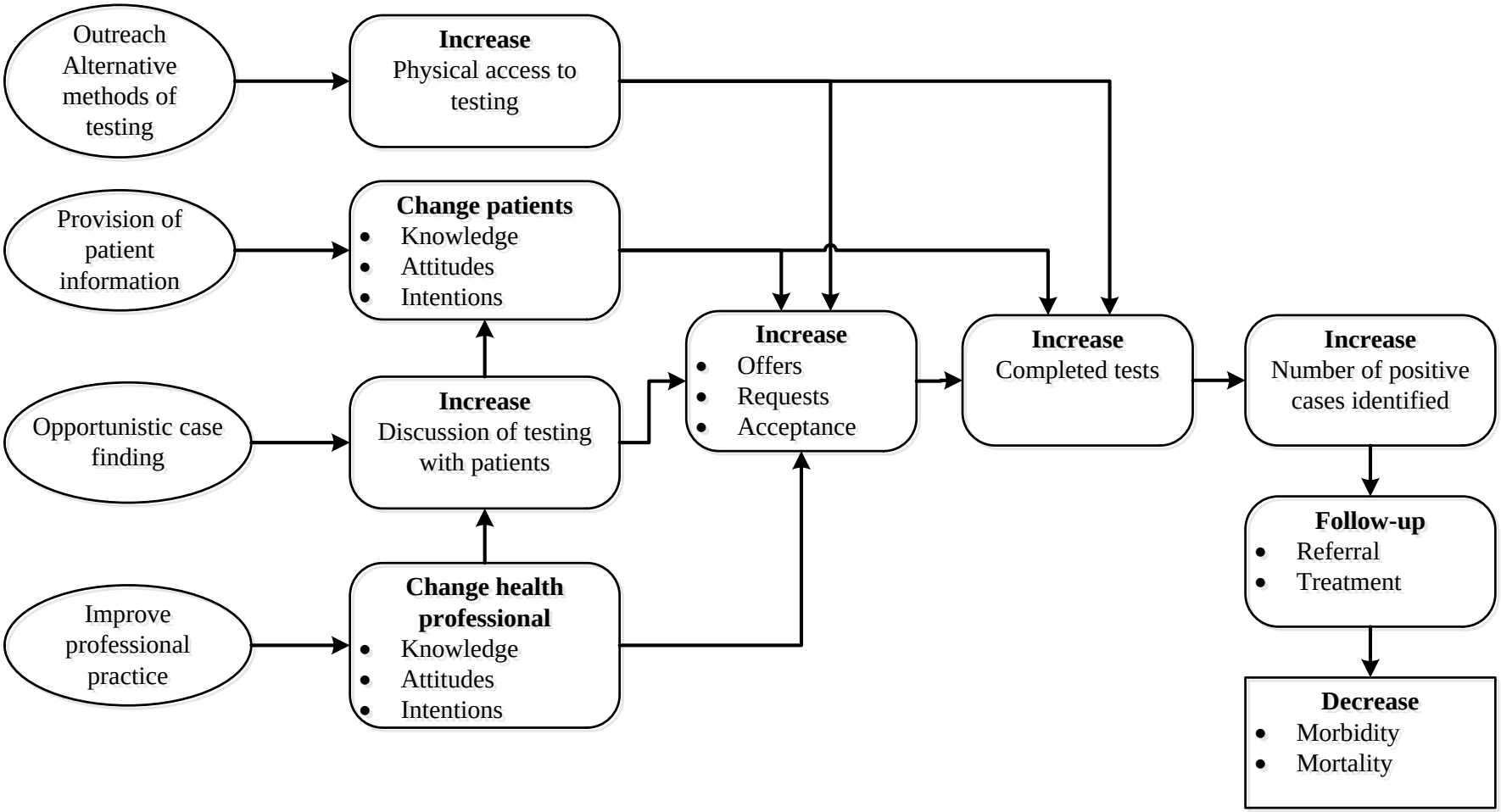


Figure 2. Logic model to explore relationships between interventions and intended outcomes