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Global Hepatitis Programme

Guideline development for Hepatitis C virus Screening, Care and Treatment in low- and middle- income countries

PICO 1: Testing

A systematic review and meta-analysis of targeted HCV antibody testing interventions

Conducted by Health Protection Scotland, Glasgow and Burnet Institute, Melbourne
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BACKGROUND

The World Health Organization estimates that between 130 and 150 million people are chronically infected with hepatitis C (HCV) virus worldwide (World Health Organization 2012), most of whom are unaware of their infection (Lavanchy, 2009). People at increased risk of HCV include people who inject drugs (PWID), and people undergoing medical procedures (including the transfusion of infected blood or blood products) in an unsafe setting (Alter et al.,1990, Villano et al., 1997). Intranasal drug use and cosmetic procedures (such as tattooing, body piercing, and manicures) have also been implicated as risk factors for HCV (Karmochine et al., 2006). The relative importance of these risk factors will vary depending on the geographical setting and population studied.

People living with chronic HCV are at increased risk of liver cirrhosis, hepatocellular carcinoma, and liver-related mortality (Grebely, 2011). It has been suggested that testing or screening interventions to detect HCV (in order to facilitate earlier access to HCV treatment and care), may prevent or reduce the risk of liver-related complications (World Health Organization 2012). The purpose of this review was to investigate the effectiveness of targeted HCV testing interventions, in terms of case detection, referral to HCV treatment and care, and the prevention of liver-related morbidity and mortality.

METHODS

Narrative review question:

Who should be tested for HCV antibodies?

PICO question:

Population: People with a history of behaviours or exposures that place them at increased risk of HCV infection

Intervention: Targeted HCV antibody testing. “Targeted” means testing of individuals based either on their being part of a defined risk group (e.g. PWID, people living with HIV) or through questions to elicit a history of HCV-risk behaviours

Comparison: Symptomatic HCV antibody testing or no targeted HCV antibody testing. “Symptomatic testing” means antibody testing based on the presence of liver-related signs or symptoms.

Outcomes: Number of HCV antibody tests, number of HCV antibody positive tests, number of referrals to a specialist*, number attending a specialist**, number commencing treatment for HCV,

number of cases of HCV transmission, HCV disease progression (liver cirrhosis, hepatocellular carcinoma, decompensated cirrhosis), sustained virological response (SVR), quality of life, all-cause mortality

***Study type/limits**:* Experimental or observational studies published between 1st January 1994 and 15th March 2013

* Defined as number of individuals who were referred to a HCV specialist, regardless of whether they actually attended
** Defined as at least one attendance at a HCV specialist appointment during the period of follow-up

Search strategy:

A systematic review was carried out for relevant articles in any language, using the following databases and information sources:

- Ovid MEDLINE, Ovid EMBASE, LILACS, and the Cochrane Library of Systematic reviews
- The Centre for Reviews and Dissemination Database (which includes the NHS Economic Evaluations Database [NHS EDD], the Health Technology Assessments Database [HTA], and the Database of Abstracts of Reviews of Effects [DARE])
- The European Network of Health Economic Evaluations Database (EURONHEED).
- Reference lists of all relevant articles and reviews
- Recommendations from Guideline Development Group (GDG) members and other experts in the field
- Relevant articles identified during the conduct of the other systematic reviews

Search terms are shown in Appendix I, briefly summarized as: Hepatitis C/HCV AND test, case-finding, or screening.

Conduct of the review:

- The review was carried out using Review Manager (version 5.2; Cochrane Collaboration, Copenhagen), and GRADE profiler (version 3.6; GRADE working group) software, and complied with Cochrane methodology and PRISMA guidelines on reporting (Prospero registration number CRD42013004146).
- Due to the large number of citations, a single reviewer removed all obviously irrelevant articles on citation screening, and subsequently, two reviewers carried out the abstract and full text screening. A third reviewer was consulted on any points of difference. Review team members are listed in appendix 2.

- Although cost-effectiveness was not included as an outcome of this review, relevant cost effectiveness studies were reviewed to check for any unpublished empirical data that met the PICO criteria.
- Foreign language articles were translated online using Google Translate, with additional interpretation sought from the primary authors as required.
- Missing data on outcomes of interest were requested from primary authors, with each author contacted twice in the case of non-response.

Quality appraisal:

Studies were assessed as having a low, high, or unclear level of bias using the Cochrane Risk of Bias assessment tool.

Data extraction:

Data were extracted from each study by the primary reviewer, and checked by the secondary reviewer. The following data were extracted, where available:

- Study characteristics: country, study design;
- Study population;
- Participant characteristics: age, sex, ethnicity, HIV co-infection;
- Setting: GP, hospital, alcohol and drug services, harm reduction services, sexual health clinics;
- Inclusion/exclusion criteria for study;
- Sample size;
- Intervention group: selection and characteristics of intervention group, prevalence of HCV among those tested;
- Intervention: type of HCV antibody test used (laboratory versus rapid testing), delivered by healthcare professional/drug support worker/ancillary staff, year or time period of intervention delivered, costs of delivery;
- Intervention subgroup: 'Direct' interventions were defined as interventions where a health or social care provider was given 'in-practice' support to offer risk assessment and/or HCV testing. 'General' interventions comprised of 'out-of practice' interventions, for example, invitations to information sessions for care providers or people at risk, leaflets or posters on HCV testing, or TV/radio awareness-raising campaigns;
- Comparison group: selection and characteristics of comparison group;

- Analysis: number offered intervention, number accepted intervention, reason for refusal, time to follow-up, statistical analysis, primary outcomes of study, secondary outcomes of study;
- Results: number of HCV antibody tests, number of HCV antibody positive tests, number of referrals to a specialist, number attending a specialist, number commencing treatment for HCV, number of cases of HCV transmission, HCV disease progression (liver cirrhosis, hepatocellular carcinoma, decompensated cirrhosis), sustained virological response (SVR), quality of life, all-cause mortality in the intervention group and the comparison group.

GRADE process:

The quality of the body of evidence for each outcome was assessed using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. GRADE rates the quality of evidence for each outcome of interest as high, moderate, low, or very low, depending on a number of criteria, including study design, study quality, study consistency (the similarity of estimates of effect across studies) and study directness (the extent to which the evidence is relevant to the population, intervention, and outcome of interest).

Population denominators:

Two different population denominators were used:

- The population eligible for testing. This varied across studies, from the number of people residing in the region where the intervention took place, to the number of people attending a specific service who were exposed to the intervention.
- The population who were HCV antibody positive. This was estimated using study-specific HCV antibody prevalence (the number of positive tests/total number of tests conducted in the *intervention* group within each study). The rationale for using those tested in the intervention group to estimate prevalence was that:
    - In most cases, there was more HCV testing in the intervention group, therefore providing a better estimate of HCV prevalence
    - HCV testing in the comparison group was more likely to be due to symptomatic testing, and would therefore lead to an over-estimation of HCV prevalence
    - For a small number of studies, HCV prevalence in the comparison group was not available.

Sensitivity analyses were conducted to assess the effect of changing the population denominator (see below).

Data synthesis: Calculation of relative risks

Random effects meta-analyses were carried out to calculate pooled effect sizes for: being tested for HCV antibodies, testing positive for HCV antibodies, being referred to a specialist, attending a specialist appointment, commencing treatment, achieving an SVR, and all-cause mortality, in populations who were exposed to a HCV testing intervention, compared to populations that were not exposed.

Investigation of heterogeneity:

Subgroup meta-analyses were carried out to calculate pooled estimates of:

- The pooled relative risk of each outcome among those who were exposed to a 'direct' intervention (health or social care service provided with in-practice support to offer risk assessment and HCV testing) compared to populations exposed to a 'general' intervention (invitations to information sessions for care providers or people at risk, leaflets or posters on HCV testing, TV/radio awareness-raising campaigns). For outcomes where there were only a small number of studies (referral, attendance, treatment, SVR, and all-cause mortality), results were presented for all studies combined rather than in subgroups.

Sensitivity analyses were carried out as follows:

-To assess the effect of using different denominators (the estimated HCV antibody positive population versus the population eligible for testing) on the pooled effect size.

-To assess the effect of different study designs (RCTs versus non-RCTs) on the pooled effect size. For outcomes where sensitivity analysis suggested that the inclusion of non-RCT evidence might over-estimate the pooled effect size, the analysis was restricted to RCTs only.

Further investigation of heterogeneity was considered inappropriate, given the small number of studies included in the review.

Data synthesis: Calculation of absolute risks

GRADE profiler was used to calculate the anticipated absolute effects of HCV testing interventions among the HCV antibody positive population, and among two hypothetical populations with HCV prevalence of 10% and 50%.

RESULTS

The literature search identified a total of 10,024 citations (Figure 1). Initial review excluded 3730 duplicates and 4471 irrelevant citations. Subsequent screening by title and abstract excluded a further 1544 citations which did not meet population, intervention, comparison, and at least one outcome criteria. Two hundred and seventy-nine abstracts advanced to full text review, of which 13 full text articles directly met the PICO criteria. A further 3 full text articles indirectly met the PICO criteria, in that they provided indirect evidence related to one outcome (HCV transmission) that was not covered by the direct evidence.

Direct evidence

Of 13 full text articles meeting the PICO, 3 articles (Helsper 2012, Litwin 2012, Sahajian 2011) reported on two different studies within the same article; therefore there were 16 studies in total. Characteristics of each of the 16 studies are described in Table 1. There were five cluster randomised controlled trials (RCT) (Cullen et al., 2006, Hickman et al., 2007, Roudot-Thoraval et al., 2000, Sahajian et al., 2011a, and Sahajian et al.,2011b), four non-randomised controlled trials (Anderson et al., 2006, Cullen et al., 2012, Helsper et al., 2010, Lewis et al., 2012), three before/after studies (Litwin et al., 2012a, Litwin et al., 2012b, Lacey et al., 2007), and four time series analyses (Defossez et al., 2008, Helsper et al., 2012a, Helsper et al., 2012b, Sahajian et al., 2004).
There were twelve studies that reported on direct HCV testing interventions (Anderson et al., 2009, Cullen et al., 2006, Cullen et al., 2012, Helsper et al., 2010, Helsper et al., 2012b, Hickman et al., 2008, Lacey et al., 2007, Lewis et al., 2012, Litwin et al., 2012a, Litwin et al., 2012b, Sahajian et al., 2011a, Sahajian et al., 2011b) and four studies that reported on general HCV testing interventions (Defossez et al., 2008, Helsper et al., 2012a, Roudot-Thouraval et al., 2000, Sahajian et al., 2004).

Eight studies compared a population exposed to a HCV testing intervention and a population in a different setting or region (e.g. another health centre or area of residence) during the same time period, who were not exposed to the intervention (Anderson et al., 2006, Cullen et al., 2006, Cullen et al., 2012, Helsper et al., 2010, Hickman et al., 2008, Roudot-Thoraval et al., 2000, Sahajian et al., 2011a, Sahajian et al., 2011b). Seven studies compared a population exposed to a HCV testing intervention and a population in the same setting or region prior to the rollout of the intervention (Defossez et al., 2008, Helsper et al., 2012a, Helsper et al., 2012b, Lacey et al., 2007, Litwin et al., 2012a, Litwin et al., 2012b, Sahajia et al., 2004). One study (Lewis et al., 2012) compared a 'direct' intervention (phone and letter invitations to participate in the HCV testing intervention) to a

'general' intervention (leaflets and posters distributed to local mosques). A sensitivity analysis including and excluding Lewis et al.,2012 had minimal impact on the pooled effect size (ES) (Appendix IV). Therefore, the Lewis et al study was included in the meta-analyses, and was assigned to the 'direct' intervention subgroup.

Data synthesis

Results of sensitivity analyses:

The use of different population denominators (the estimated HCV antibody positive population versus the population eligible for testing) had minimal impact on pooled effect size (Appendix II). Therefore, the population denominator that was most clinically appropriate to each outcome was selected, as follows:

- For the number of HCV antibody tests, and the number of positive HCV antibody tests, the denominator selected was the population eligible for testing.
- For all outcomes (referral/attendance at specialist appointment, treatment, SVR) where HCV antibody positivity was a pre-requisite for achieving that outcome, the denominator selected was the estimated HCV antibody positive population.

Results of the sensitivity analysis by study design are shown in Appendix III. For two outcomes (referral to specialist, and attendance at specialist), the inclusion of non-RCT evidence potentially over-estimated the effect size, and therefore the meta-analyses for these outcomes were restricted to RCT evidence.

Number of HCV antibody tests:

HCV testing interventions were associated with increased testing for HCV (effect size [ES] 2.90, 95% confidence interval [CI] 2.01, 4.17, I^2 = 100%) compared to no testing intervention. Direct testing strategies were more successful than general testing strategies in increasing HCV testing uptake (ES 3.47 95% CI 2.52, 4.79, I^2 = 94% and ES 1.47, 95% CI 0.71, 3.03, I^2 =100% respectively).

Number of HCV antibody positive cases detected:

HCV testing interventions were associated with increased detection of HCV antibody positive cases (ES 1.67, 95% CI 1.28, 2.20, I^2= 76%). Direct testing strategies were more successful than general testing strategies in increasing the number of HCV antibody positive cases detected (ES 2.31, 95% CI 1.47, 3.62, I^2 =79%, and RR 1.26, 95% CI 0.97, 1.64, I^2 =58% respectively).

Number referred to and attending a specialist for HCV:

HCV testing interventions were associated with increased referral to a specialist (ES 3.01, 95% CI 1.79, 5.07, I^2= N/A, 1 study), and increased attendance at specialist appointments (ES 3.66, 95% 1.92, 6.99, I^2 = N/A, 1 study), compared to no testing intervention.

Number commencing treatment and/or achieving a Sustained Virological Response (SVR):

HCV testing interventions were associated with a non-significantly increased chance of commencing treatment (ES 3.02, 95% CI 0.90, 10.15, I^2= 0%), and an equal chance of achieving an SVR (ES 1.34, 95% CI 0.25, 7.11, I^2=0%), compared to no HCV testing intervention.

All-cause mortality:

There was no significant difference in all-cause mortality between populations who were exposed to an HCV testing intervention, and populations that were not (ES 0.89, 95% CI 0.06, 13.95, I^2 = N/A, 1 study).

Absolute effects of HCV testing interventions:

The anticipated absolute effects of HCV testing interventions are shown in Tables 2a and 2b. The anticipated absolute effects of HCV testing interventions among two hypothetical populations (with HCV prevalence of 10% and 50%), are shown in Table 2c.

Indirect evidence

Number of cases of HCV transmission:

There were no studies that compared HCV transmission among populations exposed or not exposed to a HCV testing intervention. However, three studies provided indirect evidence on injecting behaviour after receiving a test for HCV.

Tsui et al. (2009) prospectively examined a cohort of 112 young PWID after HCV seroconversion. There was no significant change in self-reported injecting, syringe lending, or paraphernalia sharing at 12 months post seroconversion (p=0.75, p=0.07, p=0.45 respectively).

Ompad et al. (2002) compared injecting behaviour among 104 young PWID who tested either HCV antibody negative or HCV antibody positive. At six month follow-up, there was no significant difference in self-reported needle, drug cooker, cotton filters, or rinse water sharing between those who tested HCV antibody positive and those who tested HCV antibody negative (p=0.83, p=0.42, p=0.96, p=0.57 respectively).

Aitken et al. (2002) prospectively followed 47 PWID who received peer outreach testing and counselling. Of 20 PWID who returned for follow-up (mean 3 months), the number who reported receptive injecting equipment sharing decreased from five to two, and mean use of new needles/syringes increased from 60% to 84%.

CONCLUSIONS

HCV testing interventions were effective in increasing the number of HCV antibody positive cases detected, and the number of attendances and referrals to specialist care. Testing interventions were associated with a borderline significant increase in HCV treatment commencement, but this was not reflected in an increased chance of SVR. This may be due to the short period of follow-up used by most of the studies.

Implications for practice

Direct HCV testing strategies were more effective than general strategies in increasing the number of tests, and in detecting HCV antibody positive cases. However, decisions regarding which testing strategy to use should also take into account the relative workload and costs involved in direct compared to general strategies.

Implications for research

There is a lack of evidence for the effectiveness of HCV testing interventions with regards to treatment outcomes and HCV-related morbidity and mortality. Further research in this area should focus on the longer-term outcomes of testing interventions for HCV.

FIGURES

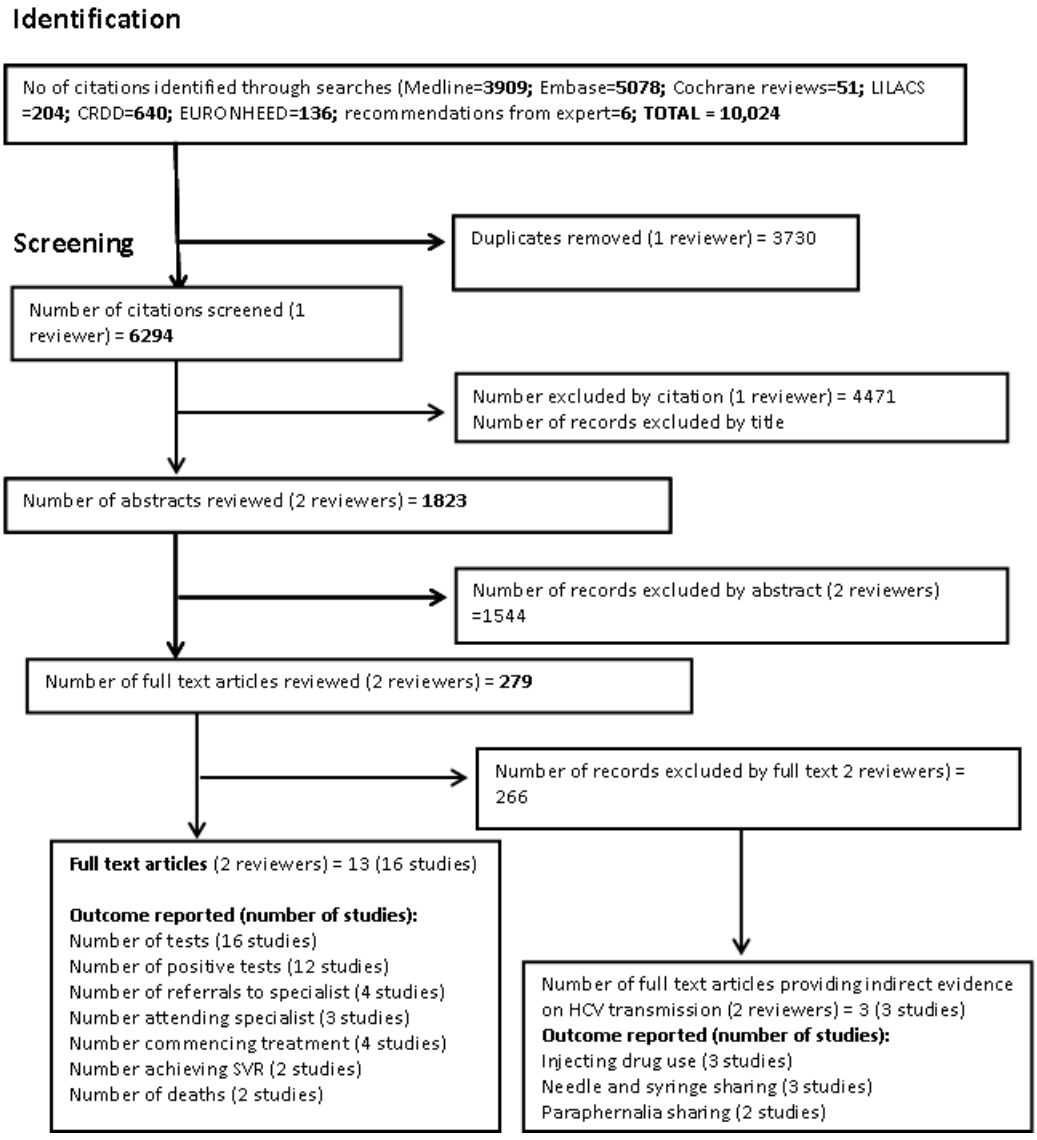
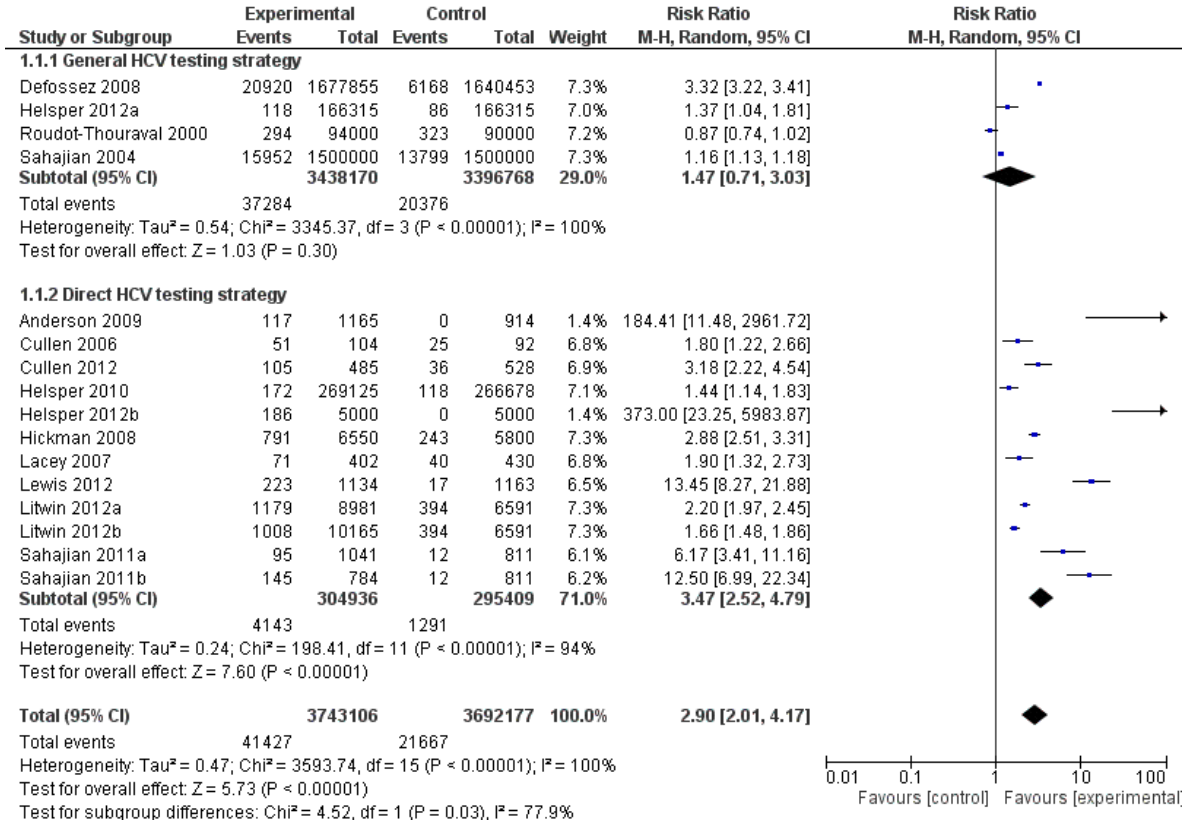


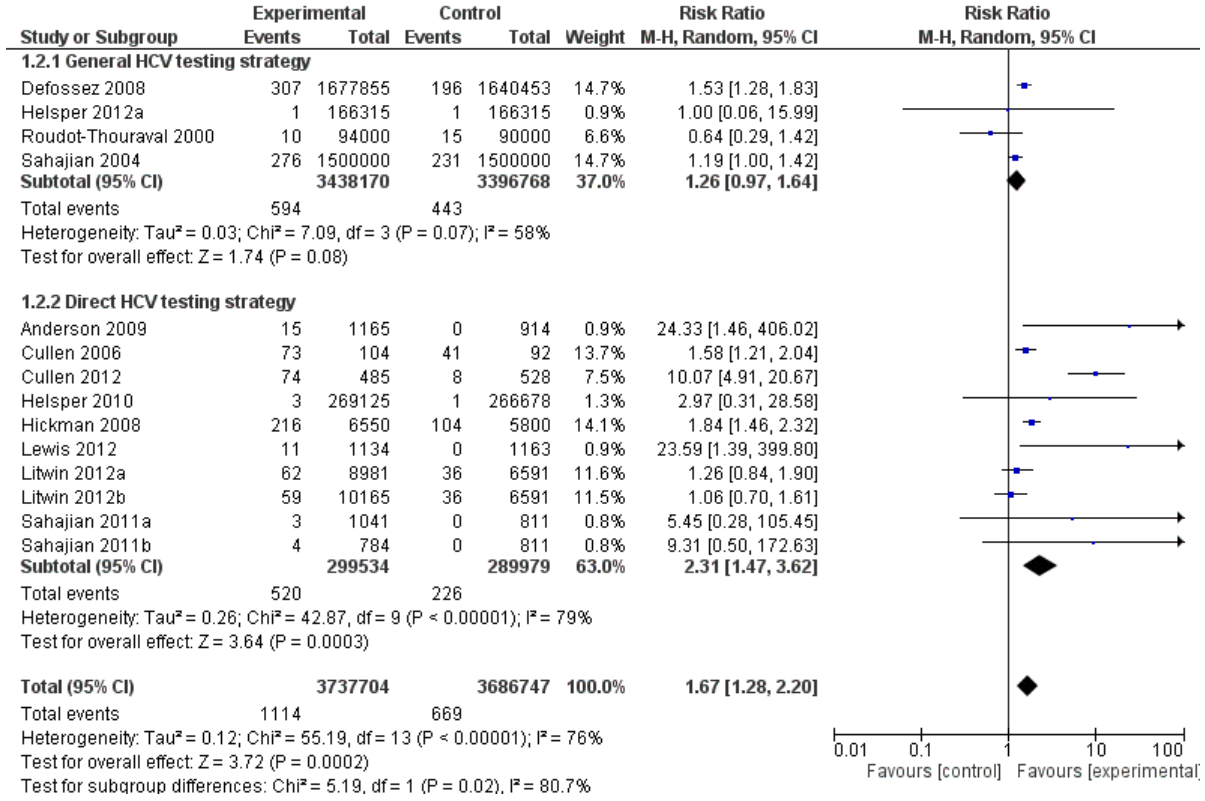
Figure 1: Flowchart for the Systematic Review

Figure 2: Forest plot of comparison: HCV testing intervention versus no intervention, outcome: HCV antibody tests among those eligible for testing



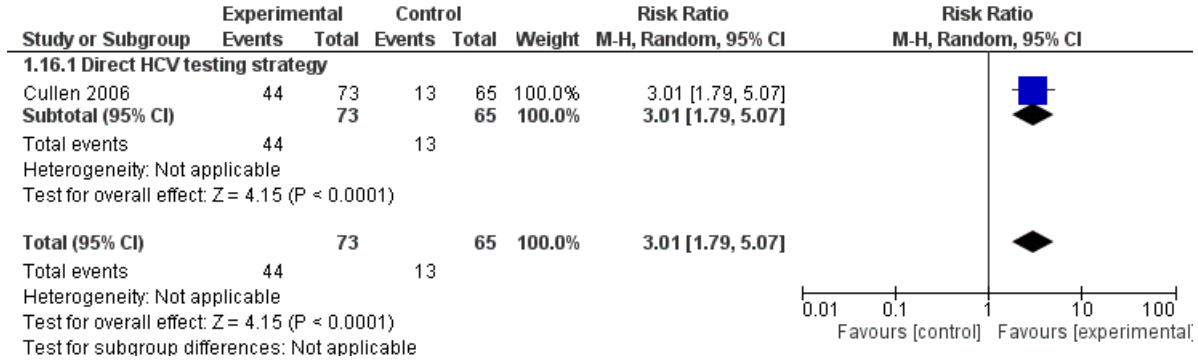
Note: sensitivity analyses investigating effect size (ES) by study design produced the following pooled estimates: Restricted to RCT: ES 2.70 (95% CI 1.44, 5.05) I^2 = 97%; restricted to non-RCTs: 3.08 (95% CI 1.90, 4.98) I^2 = 100%. Given the similarity in pooled effect sizes and heterogeneity in each group, all study designs were included for this outcome.

Figure 3: Forest plot of comparison: HCV testing intervention versus no intervention, outcome: HCV antibody positive cases detected among those eligible for testing



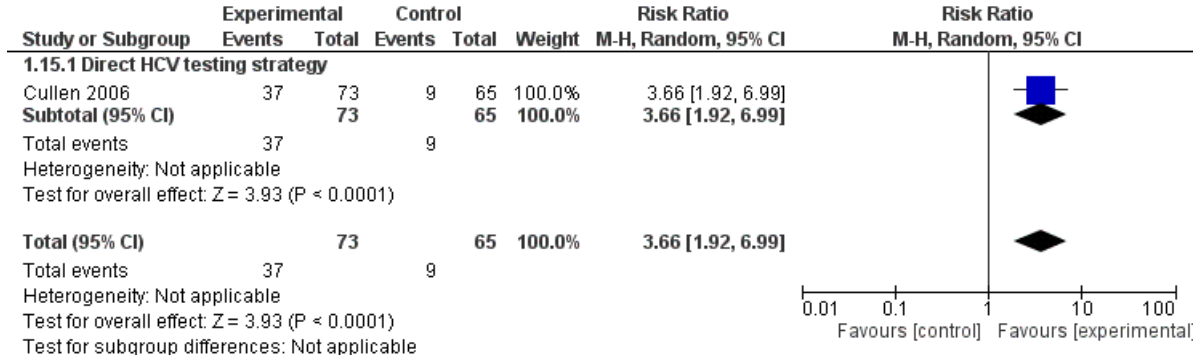
Note: sensitivity analyses investigating effect size (ES) by study design produced the following pooled estimates: Restricted to RCT: ES 1.58 (95% CI 1.14, 2.18) I^2 = 42%; restricted to non-RCTs: 1.85 (95% CI 1.23, 2.79) I^2 = 84%. Given the similarity in pooled effect sizes and heterogeneity in each group, all study designs were included for this outcome.

Figure 4: Forest plot of comparison: HCV testing intervention versus no intervention, outcome: referrals to a specialist among the estimated HCV antibody positive population



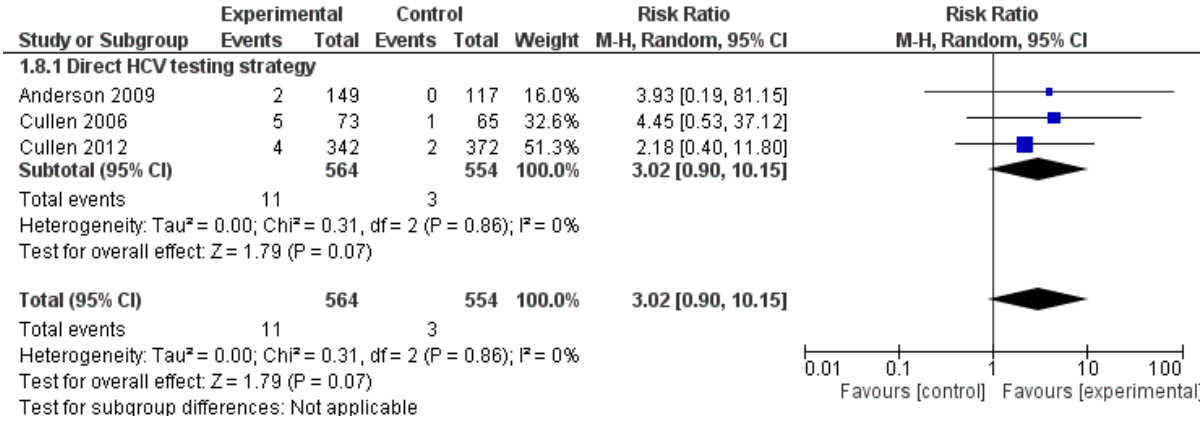
Note: sensitivity analyses investigating effect size (ES) by study design produced the following pooled estimates:
All studies: ES 6.28 (95% CI 1.81, 21.76) I^2 = 67%; Restricted to RCT: ES 3.01 (95% CI 1.79, 5.07) I^2 =N/A, 1 study; restricted to non-RCTs: 12.06 (95% CI 4.07, 35.71) I^2 = 0%. Given that the RCT evidence was judged to be high quality, and that the inclusion of non-RCT evidence risked over-estimating the effect size, the analysis for this outcome was restricted to RCT evidence only.

Figure 5: Forest plot of comparison: HCV testing intervention versus no intervention, outcome: attendance at specialist appointment among the estimated HCV antibody positive population



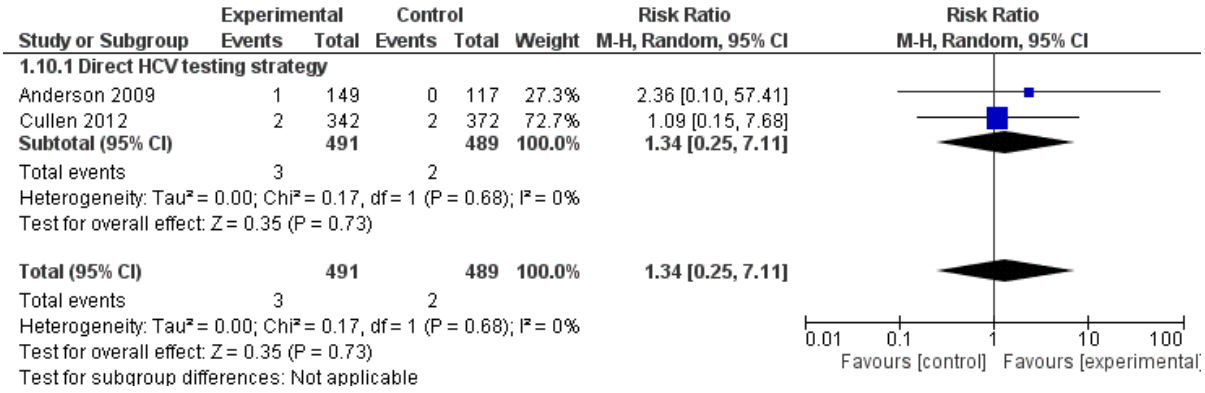
Note: sensitivity analyses investigating effect size (ES) by study design produced the following pooled estimates:
All studies: ES 6.30 (95% CI 2.24, 17.71) I^2 = 42%; Restricted to RCT: ES 3.66 (95% CI 1.92, 6.99) I^2 = N/A; restricted to non-RCTs: 13.03 (95% CI 3.61, 47.00) I^2 = 0%. Given that the RCT evidence was judged to be high quality, and that the inclusion of non-RCT evidence risked over-estimating the effect size, the analysis for this outcome was restricted to RCT evidence only.

Figure 6: Forest plot of comparison: HCV testing intervention versus no intervention, outcome: commencing treatment among the estimated HCV antibody positive population



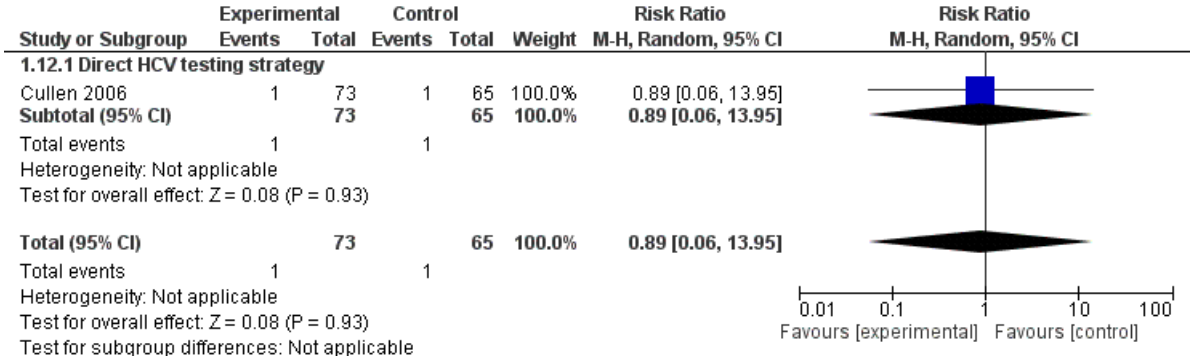
Note: sensitivity analyses investigating effect size (ES) by study design produced the following pooled estimates: Restricted to RCT: ES 4.45 (95% CI 0.53, 37.12) I^2 = N/A, 1 study; restricted to non-RCTs: 2.50 (95% CI 0.57, 10.96) I^2 = 0%. Given the similarity in pooled effect sizes across the two groups, all studies were included in the analysis for this outcome.

Figure 7: Forest plot of comparison: HCV testing intervention versus no intervention, outcome: achieving SVR among the estimated HCV antibody positive population



Note: non-RCT evidence only was available for this outcome.

Figure 8: Forest plot of comparison: HCV testing intervention versus no intervention, outcome: all-cause mortality among the estimated HCV antibody positive population*



*No deaths were observed, so the relative risk calculation approximates events to =1 in both the intervention and comparison arms.
Note: RCT evidence only was available for this outcome

TABLES

Table 1: Direct evidence

STUDY	**Anderson et al., 2006**
PARTICIPANTS	Setting and location: Two General Practices in Scotland, UK Intervention period: November 2003 – April 2004 Population: The eligible population was 2079 individuals aged 30-54 years registered with two General Practices serving an area of high socio-economic deprivation. Inclusion/exclusion criteria: Individuals with an existing diagnosis of HCV, or where offering a test was not clinically appropriate, were excluded. Study population characteristics: 53% male
HCV ANTIBODY PREVALENCE	12.8% among those tested in the intervention group
METHODS	Study design and duration: Non-randomised controlled trial, four years of follow-up Loss to follow-up: 7% of those tested in the intervention group
INTERVENTIONS	People attending non-urgent GP appointments were offered an HCV test and given an information leaflet. Those accepting the offer could immediately attend the testing and counselling appointment, or return at a later date. Routine venepuncture or oral fluid testing were offered. Individuals testing HCV RNA positive were referred to a single Hepatology Unit for further management. Individuals attending a comparison GP practice (which was situated within the same Health Centre building) were not exposed to the intervention, and received routine care.
OUTCOMES	Of 1165 eligible patients in the intervention group, 117 were tested, 15 were HCV antibody positive, 11 attended a specialist appointment, and 1 achieved an SVR. Of 914 eligible patients in the comparison group, 0 were tested.
HEADLINE FINDING OF STUDY	While non-targeted HCV screening in the general practice setting can detect infected former people who inject drugs (PWID), the low diagnostic yield among non-PWID limited the effectiveness of the intervention. The low uptake of treatment among chronically infected persons four years after diagnosis demonstrates the difficulties in clinically managing these individuals.
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation? Not randomised Allocation concealment? No Blinding? Outcome is explicitly defined, and therefore the lack of blinding was unlikely to affect outcome Incomplete outcome data addressed? Yes Free of selective reporting? Yes Free of other bias? Yes
SUMMARY	HIGH RISK OF BIAS

STUDY	**Cullen et al., 2006**
PARTICIPANTS	Setting and location: 25 General Practices in Ireland Intervention period: Not stated Population: 196 individuals receiving methadone treatment from their GP. Inclusion/exclusion criteria: A small number of patients where consent could not be obtained to access medical notes were excluded. Study population characteristics: 72 % male
HCV ANTIBODY PREVALENCE	70.2% among the intervention group. It was not possible to calculate prevalence among those tested in the intervention group, because the total number of tests was not recorded.
METHODS	Study design and duration: Cluster randomised controlled trial, six months duration Loss to follow-up: None – data collection was from GP records
INTERVENTIONS	Liaison support nurse discussed screening practice guidelines with all practice staff, provided clinical and administrative support, liaised with specialist hepatology and addiction services, and carried out counselling and testing at practices. Control practices continued with routine care.
OUTCOMES	Of 104 eligible patients in the intervention group, 51 were tested within the GP practice (plus an unknown number who were tested at locations other than their GP practice and were referred back to their GP if positive), 73 in total tested positive, 44 were referred, 37 attended a specialist appointment, of which 5 commenced HCV treatment. Of 92 eligible patients in the comparison group, 25 were tested within the GP practice (plus an unknown number who were tested at locations other than their GP practice and were referred back to their GP if positive), 41 in total tested positive, 13 were referred, 9 attended a specialist appointment, of which 1 commenced HCV treatment.
HEADLINE FINDING OF STUDY	General Practice has an important role in the care of people at risk of hepatitis C, and when appropriately supported can effectively implement current best practice.
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation? Yes Allocation concealment? Yes Blinding? Yes Incomplete outcome data addressed? Yes Free of selective reporting? Yes Free of other bias? Yes
SUMMARY	LOW RISK OF BIAS

STUDY	**Cullen et al., 2012**
PARTICIPANTS	Setting and location: 16 General Practices in Scotland, UK Intervention period: February – October 2007 Population: Estimated 1013 individuals aged 30-54 years (with GP records that suggested previous history of PWID) who attended 16 GPs serving an area of high socio-economic deprivation during the intervention period. Inclusion/exclusion criteria: individuals for whom offering a test was not clinically appropriate were excluded. Study population characteristics: 51% men
HCV ANTIBODY REVALENCE	70.5% among those tested in the intervention group
METHODS	Study design/duration: Non-randomised controlled trial, 3 years of follow-up Loss to follow-up: effectively zero, as follow-up information was derived from routine data
INTERVENTIONS	Eligible individuals attending non-urgent appointments were offered an HCV test and given an information leaflet. Participants returned to the practice to receive their results and post-test discussion from their GP. One GP practice received a staff seminar, and the remaining 7 GPs received HCV information. The control practices continued routine practice, and were not aware of their participation in the trial.
OUTCOMES	Of 485 eligible patients in the intervention group, 105 were tested, 74 were HCV antibody positive, 43 were PCR positive, 31 were referred, 22 attended a specialist appointment, 4 commenced treatment and 2 achieved an SVR. Of an estimated 528 eligible patients in the comparison group, 36 were tested, 8 were HCV antibody positive, 5 were PCR positive, 3 were referred, 2 attended, 2 commenced treatment and 2 achieved an SVR.
HEADLINE FINDING OF STUDY	Targeted case-finding in primary care achieved higher test uptake and diagnosis rates. However, to optimise diagnosis and referral of chronically infected individuals, alternative means of diagnosis (e.g. dried blood spots) and retention in care (e.g. outreach services) need to be explored.
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation? No Allocation concealment? No Blinding? No, but unlikely to affect outcome Incomplete outcome data addressed? Yes Free of selective reporting? Yes Free of other bias? Yes
SUMMARY	HIGH RISK OF BIAS

STUDY	**Defossez et al., 2008**
PARTICIPANTS	Setting and location: Poitou-Charentes Region, France Intervention period: June 1999 onwards Population: People residing in a single region of France, population 1.5 million Inclusion/exclusion criteria: People who had tested HCV antibody positive prior to the intervention were excluded from the numerator
HCV ANTIBODY PREVALENCE	1.5% among those tested in the intervention population
METHODS	Study design and duration: Time series analysis comparing pre-intervention (Nov- Dec 1997) with post-intervention (Feb-May 2003). Test data were obtained from >80% of HCV testing laboratories in the region. HCV clinical management data were obtained from questionnaires to the GP or specialist who had requested HCV positive tests. The questionnaire response rate was 60-70%. The clinical management questionnaire was carried out six to twelve months after the original laboratory survey. Loss to follow-up: N/A: series of cross-sectional studies
INTERVENTIONS	National anti-hepatitis C programme commenced in June 1999, which included implementation of a targeted screening programme, and improved care for HCV infected patients. The comparison group is the population of the same region prior to the rollout of the programme.
OUTCOMES	Of a population of 1,677,855 post-intervention, 20,920 were tested, 307 were HCV antibody positive. Survey data were available for 216 HCV antibody positive patients. Of these, 96 were newly diagnosed during 2003, of whom 14 commenced treatment, and 6 died. Of a population of 1,640,453 pre-intervention, 6168 were tested and 196 were HCV antibody positive. Survey data were available for 130 HCV antibody positive patients. Of these, 69 were newly diagnosed during 1997, of whom 8 commenced treatment, and 3 died. To account for the change in denominator between the laboratory-based data and the survey responses for the newly diagnosed individuals, a proportion (96/307) of the area population was used for the intervention, and 69/196 for the comparison group. This equated to 524,671 in the intervention group, and 577,506 in the control group.
HEADLINE FINDING OF STUDY	National Campaigns targeting the general public and healthcare professionals seem to have had no impact on patient management: in particular, drug users still do not receive adequate follow-up.
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation? No Allocation concealment? No Blinding? No, but unlikely to affect outcome Incomplete outcome data addressed? Yes, good coverage of regional data Free of selective reporting? Yes Free of other bias? It is not possible to know what proportion of the 'intervention group' was actually exposed to the intervention. Further, the intervention survey period was 4 months, compared to 2 months for the comparison survey period. However, it was unclear from the text whether this was done to correct for seasonal variations in testing. A sensitivity analysis was carried out to assess the impact of including and excluding the study. Including Defossez impacted on the effect size for the 'commence treatment' and 'all-cause mortality' outcomes, and therefore was removed from these analyses.

SUMMARY	HIGH RISK OF BIAS
STUDY	**Helsper et al., 2010**
PARTICIPANTS	Setting and location: General Practices in two regions of the Netherlands Intervention period: October 2007-January 2008 Population: People at increased risk of HCV attending study GP practices were targeted for the intervention. However, the denominator provided by the authors is the total population resident in the intervention and comparison regions (540,000) rather than the target population. Inclusion/exclusion criteria: GPs linked to shelters for drug and alcohol use were excluded. Study population characteristics: N/A
HCV ANTIBODY PREVALENCE	1.7% among those tested in the intervention group
METHODS	Study design and duration: Non randomised controlled trial, intervention period lasted four months. Loss to follow-up: Effectively none, due to use of routine data
INTERVENTIONS	The intervention comprised a support campaign for GPs, which included information, education sessions, and in-practice support from practice facilitators to carry out HCV risk assessment. Control practices continued with routine care. A public campaign to raise awareness of HCV, consisting of radio and newspapers advertisements, was carried out in *both* intervention and control regions during the same time period.
OUTCOMES	Of a population of 269,125 residing in the intervention area, 172 were tested, and 3 were positive. Of a population of 266,678 residing in the comparison area, 118 were tested, and 1 was positive.
HEADLINE FINDING OF STUDY	A campaign of support for primary care was cost-effective.
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation? No Allocation concealment? No Blinding? No, but unlikely to affect outcome Incomplete outcome data addressed? Yes Free of selective reporting? Yes Free of other bias? Yes
SUMMARY	HIGH RISK OF BIAS

STUDY	**Helsper et al., 2012a**
PARTICIPANTS	Setting and location: A single region of the Netherlands Intervention period: October 2007 – January 2008 Population: General population and at-risk groups residing in the Gelre-IJssel region, population 166,315 Inclusion/exclusion criteria: N/A Study population characteristics: N/A
HCV ANTIBODY PREVALENCE	0% among those tested in the intervention group. In order to estimate the total HCV antibody positive population, a prevalence of 1% among the study population was assumed.
METHODS	Study design and duration: Time series analysis (plus a cost-effectiveness study based on the results of the time series analysis). Loss to follow-up: N/A
INTERVENTIONS	Local broadcasting of radio advertisements, publishing advertisements in newspapers, distribution of specially designed posters and brochures in public areas where risk groups were expected to congregate. The comparison group were the population living in the same region prior to rollout of the intervention.
OUTCOMES	Of an estimated population of 166,315 residing in the area post-intervention, 118 were tested, and 0 were positive. Of an estimated population of 166,315 residing in the area pre-intervention, 86 were tested, and 0 were positive.
HEADLINE FINDING OF STUDY	A campaign aimed at the general public without support for primary care did not improve case-finding and was therefore not cost-effective.
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation? No Allocation concealment? No Blinding? No, but unlikely to affect outcome Incomplete outcome data addressed? Yes Free of selective reporting? Yes Free of other bias? No – it is not possible to know what proportion of the 'intervention group' were actually exposed to the intervention
SUMMARY	HIGH RISK OF BIAS

STUDY	**Helsper et al., 2012b**
PARTICIPANTS	Setting and location: Drug services in Rotterdam, the Netherlands Intervention period: May 2007 – September 2008 Population: Current or former 'hard drug users' (HDUs): total population of HDUs in geographical area of intervention was estimated at 5000 Inclusion/exclusion criteria: N/A Study population characteristics: N/A
HCV PREVALENCE	30.6% among those tested in the intervention group
METHODS	Study design and duration: Time series analysis Loss to follow-up: Effectively none, due to use of routine data
INTERVENTIONS	26 addiction care professionals were trained to provide HCV counselling, and three information meetings were held that were attended by 180 HDUs. The comparison group were the same population prior to the rollout of the intervention.
OUTCOMES	Of a population of 5000 HDUs, 186 were tested, and 57 were HCV antibody positive during the intervention. Of a population of 5000 HDUs, there was zero testing prior to the intervention. This was an assumption based on a review of Drug Services practice, as well as local Health Service Organization records. Because the number of tests was based on an assumption, no further assumptions (e.g. the number of positive tests) were made about the comparison arm.
HEADLINE FINDING OF STUDY	A campaign aimed at hard drug users was cost-effective.
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation? No Allocation concealment? No Blinding? No, but unlikely to affect outcome Incomplete outcome data addressed? Yes Free of selective reporting? Yes Free of other bias? No – it is not possible to know what proportion of the 'intervention group' were actually exposed to the intervention
SUMMARY	HIGH RISK OF BIAS

STUDY	**Hickman et al., 2007**
PARTICIPANTS	Setting and location: 14 specialist drug clinics and 6 prisons in the UK Intervention period: June 2004 – June 2005 Population: 12,350 prison inmates or drug users attending specialist drug clinics Inclusion/exclusion criteria: N/A Study population characteristics: N/A
HCV ANTIBODY PREVALENCE	27.3% among those tested in the intervention group
METHODS	Study design and duration: Cluster randomised controlled trial Loss to follow-up: Effectively none, because of use of laboratory data
INTERVENTIONS	HCV testing using dried blood spot (DBS) testing. Half day introduction to the intervention that included staff training and information on DBS, plus on-going support from local specialist HCV nurses. The comparison group (matched prisons or drug services) received routine care.
OUTCOMES	Of a population of 6550 in the intervention group, 791 were tested, and 216 were HCV antibody positive. Of a population of 5800 in the comparison group, 243 were tested, and 104 were HCV antibody positive.
HEADLINE FINDING OF STUDY	This study provides preliminary evidence that DBS may increase the uptake of HCV diagnostic testing, by increasing the opportunities for patients to be offered testing.
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation? Yes Allocation concealment? Yes Blinding? No, but unlikely to affect outcome Incomplete outcome data addressed? Yes Free of selective reporting? Yes Free of other bias? Yes
SUMMARY	LOW RISK OF BIAS

STUDY	**Lacey et al., 2007**
PARTICIPANTS	Setting and location: Inpatient psychiatry unit in a tertiary hospital, Australia Intervention period: August 2002 – January 2003 Population: 832 psychiatric inpatients admitted to a single psychiatric unit during the intervention and comparison periods. Inclusion criteria: Diagnosis of serious mental disorder, able to provide informed consent, inpatient stay of more than two days. Exclusion criteria: Known HCV infection Study population characteristics: N/A
HCV ANTIBODY PREVALENCE	19.7% among those tested in the intervention group
METHODS	Study design and duration: Before/after study (cohort) Loss to follow-up: None – use of laboratory data
INTERVENTIONS	During the intervention period, a leaflet providing information on HCV was distributed, and a research assistant facilitated education/discussion groups, and carried out counselling and testing. The comparison group comprised psychiatric inpatients admitted during the same length time period (Feb 2002-July 2002) prior to the rollout of the intervention.
OUTCOMES	Of 402 individuals in the intervention group, 71 were tested, and 14 were HCV antibody positive and referred to Infectious Diseases. Of 430 individuals in the comparison group, 40 were tested.
HEADLINE FINDING OF STUDY	An education and counselling programme can increase HCV testing among psychiatric inpatients.
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation? Not randomised Allocation concealment? No Blinding? No, but unlikely to affect outcome Incomplete outcome data addressed? Yes Free of selective reporting? Yes Free of other bias? Yes
SUMMARY	HIGH RISK OF BIAS

STUDY	**Lewis et al., 2012**
PARTICIPANTS	Setting and location: Mosques and GP practices serving the Pakistani population in the UK Intervention period: Not available Population: 2297 Pakistani patients attending local mosques in London, UK Inclusion/exclusion criteria: Not available Study population characteristics: Not available
HCV ANTIBODY PREVALENCE	4.9% among those tested in the intervention group
METHODS	Study design and duration: Non-randomised controlled trial Loss to follow-up: None
INTERVENTIONS	Patients were contacted by letter and phone to invite them to attend screening clinics at their GP surgery. This was compared to an opportunistic approach where leaflets were distributed to mosques advising them to attend clinics for testing. The inclusion/exclusion of this study in the meta-analyses was tested in the sensitivity analysis.
OUTCOMES	Of a population of 1134 in the intervention group, 223 were tested, and 11 were HCV antibody positive. Of a population of 1163 in the control group, 17 were tested, and 0 were HCV antibody positive.
HEADLINE FINDING OF STUDY	Community awareness campaigns do not directly lead to testing for viral hepatitis in at risk immigrant groups. A direct screening approach is more effective than an opportunistic screening approach in primary care.
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation? No Allocation concealment? No Blinding? No, but unlikely to affect outcome Incomplete outcome data addressed? Yes Free of selective reporting? Yes Free of other bias? Yes
SUMMARY	HIGH RISK OF BIAS

STUDY	**Litwin et al., 2012a**
PARTICIPANTS	Setting and location: Three community-based primary care clinics located in urban areas of New York, USA Intervention period: Intervention ran from November 2008 to March 2009 Population: 15,572 patients who attended one of the study practices during the intervention or comparison period. Inclusion criteria: Age > 18 years Exclusion criteria: previously tested for HCV antibodies Study population characteristics: 25% male, Race/ethnicity: 30% black
HCV ANTIBODY PREVALENCE	5.3% among those tested in the intervention group
METHODS	Study design and duration: Before/after study (cohort), 'before' period was two months, and 'after' period was five months. The difference in time periods in the two arms was accounted for in the denominator (the number of eligible individuals attending the practice during the study period). Loss to follow-up: None (use of routine data)
INTERVENTIONS	Risk based screening facilitated by providing a 'risk sticker' on notes, prompting physician to ask about HCV risk factors and to offer testing if a risk factor was present. The comparison group were individuals attending the practice prior to the intervention who received routine care.
OUTCOMES	Of 8981 individuals in the intervention group, 1179 were tested, and 62 were HCV antibody positive. Of 6591 individuals in the intervention group, 394 were tested, and 36 were HCV antibody positive.
HEADLINE FINDING OF STUDY	A 'risk-based' strategy increased the number of tests and the number of positive tests.
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation? No Allocation concealment? No Blinding? No, but unlikely to affect outcome Incomplete outcome data addressed? Yes Free of selective reporting? Yes Free of other bias? Yes
SUMMARY	HIGH RISK OF BIAS

STUDY	**Litwin et al., 2012b**
PARTICIPANTS	Setting and location: Three community-based primary care clinics located in urban areas of New York, USA Intervention period: Intervention ran from March-June 2009 Population: 16,756 patients who attended one of the study practices during the intervention or comparison period. This population refers to all patients who attended the clinics at least once during the intervention and comparison periods, *not* the number of patients who were in the correct age category. Inclusion criteria: Age > 18 years Exclusion criteria: record of previous test for HCV antibodies in medical notes. Study population characteristics: 25% male, Race/ethnicity: 30% black
HCV ANTIBODY PREVALENCE	5.9% among those tested in the intervention group
METHODS	Study design and duration: Before/after study (cohort): 'before' period was two months, and 'after' period was four months. Loss to follow-up: None (use of routine data)
INTERVENTIONS	Birth cohort-based screening, facilitated by adding a 'Birth cohort' reminder sticker on the top of each set of progress notes, asking GPs to offer HCV testing to all patients born between 1945 and 1964. The comparison group were individuals attending the practice in a period prior to the intervention.
OUTCOMES	Of 10,165 patients in the intervention group, 1008 were tested, and 59 were HCV antibody positive during the intervention. Of 6591 patients in the comparison group, 394 were tested, and 36 were HCV antibody positive during the intervention.
HEADLINE FINDING OF STUDY	A birth cohort strategy increased the number of tests, and the number of positive tests.
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation? No Allocation concealment? No Blinding? No, but unlikely to affect outcome Incomplete outcome data addressed? Yes Free of selective reporting? Yes Free of other bias? Yes. Note: the birth cohort screening took place after the risk-based screening in the same practices (Litwin et al., 2012a). However, the authors carried out further sensitivity analyses to investigate whether this would have affected the outcomes of the birth cohort intervention. These sensitivity analyses were non-significant.
SUMMARY	HIGH RISK OF BIAS

STUDY	**Roudot-Thoraval et al., 2000**
PARTICIPANTS	Setting and location: 184 General Practitioners in the Creteil region of France Intervention period: April 1997 – November 1998 Population: People attending GP appointments. Given that the only denominator information provided by the authors was the number of General Practitioners in each arm of the trial, an assumption was made that each GP had 1000 patients. Therefore, there the population of the intervention arm was estimated to be 94,000 (94 GPs), and the population of the comparison arm was estimated to be 90,000 (90 GPs). Inclusion/exclusion criteria: N/A Study population characteristics: N/A
HCV ANTIBODY PREVALENCE	3.4% among those tested in the intervention group
METHODS	Study design and duration: Randomised controlled trial Loss to follow-up: Effectively zero, as follow-up data obtained from routine sources
INTERVENTIONS	Provision of study posters and leaflets at General Practice surgeries, informing patients of the risk factors of HCV. Comparison General Practice surgeries provided routine care. All GPs (both intervention and comparison group) were invited to an information evening on hepatitis C.
OUTCOMES	Of an estimated 94,000 individuals in the intervention arm, there were 294 tests, of which 10 were HCV antibody positive. Of an estimated 90,000 individuals in the comparison arm, there were 323 tests, of which 15 were HCV antibody positive.
HEADLINE FINDING OF STUDY	The HCV antibody testing intervention had no impact on the number of tests, or the number of positive tests. GPs requested very few HCV tests, suggesting a low rate of identified risk factors in general practice.
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation? 'Random allocation' Allocation concealment? Unclear Blinding? No, but unlikely to affect outcome Incomplete outcome data addressed? Yes Free of selective reporting? Yes Free of other bias? Yes
SUMMARY	LOW RISK OF BIAS

STUDY	**Sahajian et al., 2004**
PARTICIPANTS	Setting and location: 3052 General Practitioners and specialists in private practice in the Lyon area in France Intervention period: Pre-campaign period was April 1999 to March 2000, and campaign period was April 2000 to March 2001 Population: Population of region was approximately 1.5 million. The population attending GPs and private specialists was not provided. Inclusion/exclusion criteria: N/A Study population characteristics: N/A
HCV ANTIBODY PREVALENCE	1.7% among those tested in the intervention group
METHODS	Study design and duration: time series analysis, 2 years Loss to follow-up: N/A
INTERVENTIONS	During the intervention period, a guide on screening was mailed to private practitioners, and workshops and training sessions on screening for GPs and laboratory physicians were offered. The aim of the campaign was to encourage practitioners to offer HCV tests to people at increased risk (due to a history of PWID, blood products prior to 1991, or elevated ALT levels) There was also an information campaign to the general public that included a press conference and media advertisements. The comparison group was the population of the same region prior to the screening campaign.
OUTCOMES	In the intervention population (approximately 1.5 million), there were 15,952 tests, and 276 positive tests. In the comparison group, there were 13,799 tests, and 231 positive tests.
HEADLINE FINDING OF STUDY	The HCV antibody testing intervention increased the number of tests, and there was also a small increase in the number of positive tests.
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation? No Allocation concealment? No Blinding? No, but unlikely to affect outcome Incomplete outcome data addressed? Yes Free of selective reporting? Yes Free of other bias? No – it is not possible to know what proportion of the 'intervention group' were actually exposed to the intervention
SUMMARY	HIGH RISK OF BIAS

STUDY	**Sahajian et al., 2011a**
PARTICIPANTS	Setting and location: 12 homeless hostels and shelters providing long-term accommodation in the Lyon area in France Intervention period: October 2007 – April 2009 Population: 1852 residents of homeless hostels or shelters Inclusion/exclusion criteria: Not available Study population characteristics: Not available
HCV ANTIBODY PREVALENCE	3.2% among those tested in the intervention group
METHODS	Study design and duration: Cluster randomised controlled trial, 18-month duration Loss to follow-up: None (used routine data)
INTERVENTIONS	In the intervention hostels and shelters, group information sessions were followed by referral, if interested, to a Health Centre where a medical check-up and HCV testing were carried out. The comparison hostels and shelters received routine care.
OUTCOMES	Of 1041 individuals in the intervention group, there were 95 tests, and 3 positive tests. Of 811 individuals in the comparison group, there were 12 tests, and 0 positive tests.
HEADLINE FINDING OF STUDY	Health authorities must ensure widespread screening of underprivileged people, which is more effective when conducted in shelters than in screening centres (see also Sahajian 2011b).
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation? Yes Allocation concealment? Yes Blinding? No, but unlikely to affect outcome Incomplete outcome data addressed? Yes Free of selective reporting? Yes Free of other bias? Yes
SUMMARY	LOW RISK OF BIAS

STUDY	**Sahajian et al., 2011b**
PARTICIPANTS	Setting and location: 12 homeless hostels and shelters providing long-term accommodation in the Lyon area in France Intervention period: October 2007 – April 2009 Population: 1595 residents of homeless hostels or shelters Inclusion/exclusion criteria: Not available Study population characteristics: Not available
HCV ANTIBODY PREVALENCE	2.8% among those tested in the intervention group
METHODS	Study design and duration: Cluster randomised controlled trial, 18-month duration Loss to follow-up: Effectively zero, as use of routine data
INTERVENTIONS	In the intervention hostels and shelters, group information sessions were followed by on-site medical check-ups and HCV testing for those who were interested. The comparison hostels and shelters received routine care.
OUTCOMES	Of 784 individuals in the intervention group, there were 145 tests, and 4 positive tests. Of 811 individuals in the comparison group, there were 12 tests, and 0 positive tests.
HEADLINE FINDING OF STUDY	Health authorities must ensure widespread screening of underprivileged people, which is more effective when conducted in shelters than in screening centres (see also Sahajian 2011a).
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation? Yes Allocation concealment? Yes Blinding? No, but unlikely to affect outcome Incomplete outcome data addressed? Yes Free of selective reporting? Yes Free of other bias? Yes
SUMMARY	LOW RISK OF BIAS

Table 2a: GRADE summary of findings: testing for HCV, and HCV positive cases detected among the population eligible for testing

Outcome	Subgroup	Eligible population (studies)	GRADE quality*	Effect size (95% CI)	Baseline risk per 10,000 eligible population	Anticipated absolute effects per 10,000 eligible population (95% CI)
Tested for HCV	All strategies	7,435,283 (16 studies)	MODERATE [a]	2.90 (2.01, 4.17)	59 tests conducted	112 more HCV antibody tests (from 59 more to 186 more)
	General strategy	6,834,938 (4 studies)	LOW [b]	1.47 (0.71, 3.03)	60 tests conducted	28 more HCV antibody tests (from 17 fewer to 122 more)
	Direct strategy	600,345 (12 studies)	MODERATE [c]	3.47 (2.52, 4.79)	44 tests conducted	108 more HCV antibody tests (from 66 more to 166 more)
HCV positive cases detected	All strategies	7,424,451 (14 studies)	MODERATE [d]	1.67 (1.28, 2.20)	2 cases detected	1 more case detected (from 0 more to 2 more)
	General strategy	6,834,938 (4 studies)	MODERATE [e]	1.26 (0.97, 1.64)	1 case detected	0 more cases (from 0 fewer to 1 more)
	Direct strategy	589,513 (10 studies)	MODERATE [f]	2.31 (1.47, 3.62)	8 cases detected	10 more cases detected (from 4 more to 20 more)

*Marked down for: a) inconsistency; b) inconsistency and imprecision; c) inconsistency; d) inconsistency; e) inconsistency; f) inconsistency.

Table 2b: GRADE summary of findings: management of HCV positive individuals among the estimated HCV antibody positive population

Outcome (mean follow-up)	Population (studies)	GRADE quality*	Effect size (95% CI)	Baseline risk per 10,000 HCV antibody positive population	Anticipated absolute effects per 10,000 HCV antibody positive population (95% CI)
Referral to HCV specialist (Six months)	138 (1 study)	MODERATE [a]	3.01 (1.79, 5.07)	2,000 referrals to specialist	4020 more referrals to a specialist (from 1580 more to 8140 more)
Attendance at HCV specialist (Six months)	138 (1 study)	MODERATE [b]	3.66 (1.92, 6.99)	1,380 attending a specialist	3683 more cases attending a specialist (from 1274 more to 8294 more)
Commenced treatment (Two years)	17,263 (4 studies)	MODERATE [c]	3.02 (0.90, 10.15)	54 commencing treatment	109 more commencing treatment (from 5 fewer to 495 more)
SVR (Three years six months)	980 (2 studies)	VERY LOW [d]	1.34 (0.25, 7.11)	41 achieving SVR	14 more achieving SVR (from 31 fewer to 250 more)
Morbidity	No data available				
All-cause mortality (Six months)	138 (1 study)	LOW [e]	0.89 (0.06, 13.95)	Insufficient data	Insufficient data
Quality of Life	No data available				

*Marked down for: a) sparse data; b) sparse data; c) sparse data; d) observational studies and sparse data; e) directness and sparse data.

Table 2c: Anticipated absolute effects of HCV testing interventions by population HCV prevalence

Outcome	GRADE quality	Subgroup	HCV prevalence	Anticipated absolute effects of HCV testing interventions per 10,000 population (95% CI)
HCV antibody positive cases detected	MODERATE	All strategies	10%	5 more cases detected (from 2 more to 8 more)
			50%	23 more cases detected (from 9 more to 40 more)
		Direct strategy	10%	8 more cases detected (from 3 more to 15 more)
			50%	39 more cases detected (from 14 more to 77 more)
		General strategy	10%	2 more cases detected (from 0 fewer to 5 more)
			50%	10 more cases detected (from 1 fewer to 26 more)
Referral to specialist	MODERATE	All strategies	10%	330 more cases (from 649 more to 1370 more)
			50%	2812 more cases (from 1017 more to 5935 more)
Attendance at specialist	MODERATE	All strategies	10%	289 more cases (from 100 more to 651 more)
			50%	1735 more cases (from 600 more to 3907 more)
Commenced treatment	MODERATE	All strategies	10%	13 more commencing treatment (from 1 fewer to 60 more)
			50%	39 more commencing treatment (from 2 fewer to 179 more)
SVR	VERY LOW	All strategies	10%	0 more SVRs (from 0 fewer to 4 more)
			50%	5 more SVRs (from 11 fewer to 86 more)
All-cause mortality	LOW	All strategies	10%	Insufficient data
			50%	Insufficient data

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APPENDICIES

Appendix 1: Search terms

Medline and Embase

1. *Hepatitis C/
2. HCV.ti,ab.
3. hepatitis c.ti,ab.
4. 1 or 2 or 3
5. *Mass Screening/
6. case finding.ti,ab.
7. case identification.ti,ab.
8. case detection.ti,ab.
9. screening.ti,ab.
10. test* for hepatitis C.ti,ab.
11. test* for HCV.ti,ab.
12. hepatitis C testing.ti,ab.
13. HCV testing.ti,ab.
14. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. 4 and 14
16. limit 15 to humans
17. limit 16 to yr="1994 -Current"
18. remove duplicates from 17

Appendix 2: Sensitivity analyses examining the effect of denominator on pooled effect size

Outcome	Subgroup	Denominator used	Pooled effect size	I^2
Referrals to specialist	Total	Population eligible for testing	6.23 (1.84, 21.09)	65%
		HCV antibody positive population	6.28 (1.81, 21.76)	67%
	Direct strategy	Population eligible for testing	6.23 (1.84, 21.09)	65%
		HCV antibody positive population	6.28 (1.81, 21.76)	67%
	General strategy	Population eligible for testing	No studies	-
		HCV antibody positive population	No studies	-
Attendances at specialist	Total	Population eligible for testing	6.26 (2.25, 17.38)	40%
		HCV antibody positive population	6.30 (2.24, 17.71)	42%
	Direct strategy	Population eligible for testing	6.26 (2.25, 17.38)	40%
		HCV antibody positive population	6.30 (2.24, 17.71)	42%
	General strategy	Population eligible for testing	No studies	-
		HCV antibody positive population	No studies	-
Commenced treatment	Total	Population eligible for testing	3.01 (0.89, 10.15)	0%
		HCV antibody positive population	3.02 (0.90, 10.15)	0%
	Direct strategy	Population eligible for testing	3.01 (0.89, 10.15)	0%
		HCV antibody positive population	3.02 (0.90, 10.15)	0%
	General strategy	Population eligible for testing	No studies	-
		HCV antibody positive population	No studies	-
SVR	Total	Population eligible for testing	1.34 (0.25, 7.13)	0%
		HCV antibody positive population	1.34 (0.25, 7.11)	0%
	Direct strategy	Population eligible for testing	1.34 (0.25, 7.13)	0%
		HCV antibody positive population	1.34 (0.25, 7.11)	0%
	General strategy	Population eligible for testing	No studies	-
		HCV antibody positive population	No studies	-
Deaths	Total	Population eligible for testing	0.88 (0.06, 13.94)	1 study
		HCV antibody positive population	0.89 (0.06, 13.95)	1 study
	Direct strategy	Population eligible for testing	0.88 (0.06, 13.94)	1 study
		HCV antibody positive population	0.89 (0.06, 13.95)	1 study
	General strategy	Population eligible for testing	No studies	-
		HCV antibody positive population	No studies	-

Appendix 3: Sensitivity analyses examining the effect of study design on pooled effect size

Outcome	Subgroup	Study design	Pooled effect size*	I^2	Comment/Decision
Number of HCV antibody tests	All strategies	**All studies**	**2.90 (2.01, 4.17)**	**100%**	Stratification by study design has minimal impact on effect size or heterogeneity: include all study designs in the data synthesis for this outcome.
		RCT	2.70 (1.44, 5.05)	97%	
		Non-RCT	3.08 (1.90, 4.98)	100%	
	Direct strategy	**All studies**	**3.47 (2.52, 4.79)**	**94%**	Stratification by study design has minimal impact on effect size or heterogeneity: include all study designs in the data synthesis for this outcome.
		RCT	3.38 (1.92, 5.93)	94%	
		Non-RCT	3.73 (2.34, 5.96)	95%	
	General strategy	**All studies**	**1.47 (0.71, 3.03)**	**100%**	The inclusion of non-RCTs changes the direction of the pooled effect size, but both results remain non-significant: include all study designs in the data synthesis for this outcome.
		RCT	0.87 (0.74, 1.02)	1 study	
		Non-RCT	1.74 (0.75, 4.07)	100%	
Number of HCV antibody cases detected	All strategies	**All studies**	**1.67 (1.28, 2.20)**	**76%**	The inclusion of non-RCTs increases heterogeneity but has minimal impact on the pooled effect size: include all study designs in the data synthesis for this outcome.
		RCT	1.58 (1.14,2.18)	42%	
		Non-RCT	1.85 (1.23, 2.79)	84%	
	Direct strategy	**All studies**	**2.31 (1.47, 3.62)**	**79%**	The inclusion of non-RCTs has a minimal effect on the pooled effect size: include all study designs in the data synthesis for this outcome.
		RCT	1.74 (1.47, 2.07)	0%	
		Non-RCT	3.65 (1.22, 10.93)	90%	
	General strategy	**All studies**	**1.26 (0.97, 1.64)**	**58%**	The inclusion of non-RCTs changes the direction of the pooled effect size, but both results are non-significant: include all study designs in the data synthesis for this outcome.
		RCT	0.64 (0.29, 1.42)	1 study	
		Non-RCT	1.35 (1.09, 1.66)	48%	
Referral to HCV specialist among antibody positive population	All strategies	All studies	6.28 (1.81, 21.76)	67%	Inclusion of non-RCTs may over-estimate the pooled effect size and increases heterogeneity: include RCTs only in the data synthesis for this outcome.
		RCT	**3.01 (1.79, 5.07)**	**1 study**	
		Non-RCT	12.06 (4.07, 35.71)	0%	
Attendance at HCV specialist	All strategies	All studies	6.30 (2.24, 17.71)	42%	Inclusion of non-RCTs may over-estimate the pooled effect size and increases heterogeneity: include RCTs only in the data synthesis for this outcome.
		RCT	**3.66 (1.92, 6.99)**	**1 study**	
		Non-RCT	13.03 (3.61, 47.00)	0%	
HCV treatment commenced	All strategies	**All studies**	**3.02 (0.90, 10.15)**	**0%**	Inclusion of non-RCTs has no effect on heterogeneity and produces a more conservative effect size: include all study designs for this outcome.
		RCT	4.45 (0.53, 37.12)	1 study	
		Non-RCT	2.50 (0.57, 10.96)	0%	
SVR	All strategies	**All studies**	**1.34 (0.25, 7.11)**	**100%**	Only non-RCT evidence available for this outcome, therefore include non-RCTs
		RCT	No studies	-	
		Non-RCT	1.34 (0.25, 7.11)	0%	
All-cause mortality	All strategies	**All studies**	**0.89 (0.06, 13.95)**	**1 study**	Only one study (an RCT) reported on this outcome: use 'all studies'.
		RCT	0.89 (0.06, 13.95)	1 study	
		Non-RCT	No studies	-	

*The pooled effect size selected for use in the analyses is shown in bold type

Appendix 4: Sensitivity analysis including/excluding specific studies

Outcome	Subgroup	Inclusion	Pooled effect size	I^2
Number of HCV antibody tests	All strategies	Lewis et al., 2012 included	**2.90 (2.01, 4.17)**	**100%**
		Lewis et al., 2012 excluded	2.60 (1.79, 3.77)	100%
	Direct strategy	Lewis et al., 2012 included	**3.47 (2.52, 4.79)**	**94%**
		Lewis et al., 2012 excluded	2.91 (2.18, 3.88)	93%
HCV antibody positive cases detected	All strategies	Lewis et al., 2012 included	**1.67 (1.28, 2.20)**	**76%**
		Lewis et al., 2012 excluded	1.63 (1.25, 2.12)	79%
	Direct strategy	Lewis et al., 2012 included	**2.31 (1.47, 3.62)**	**79%**
		Lewis et al., 2012 excluded	2.16 (1.39, 3.36)	79%
Number of HCV antibody tests	All strategies	Defossez et al., 2008 included	**2.90 (2.01, 4.17)**	**100%**
		Defossez et al., 2008 excluded	2.65 (1.99, 3.52)	98%
HCV antibody positive cases detected	All strategies	Defossez et al., 2008 included	**1.67 (1.28, 2.20)**	**76%**
		Defossez et al., 2008 excluded	1.77 (1.25, 2.49)	78%
Commenced treatment	All strategies	Defossez et al., 2008 included	2.25 (1.11, 4.56)	0%
		Defossez et al., 2008 excluded	**3.02 (0.90, 10.15)**	**0%**
All-cause mortality	All strategies	Defossez et al., 2008 included	1.84 (0.53, 6.34)	0%
		Defossez et al., 2008 excluded	**0.89 (0.06, 13.95)**	**1 study**

*The pooled effect size selected for use in the analyses is shown in bold type

Appendix 5: GRADE outcome assessments

Testing for HCV antibodies: all strategies

GRADE assessment criteria		Assessment	GRADE score	GRADE running total
Type of evidence		*5 RCTs, 9 non-RCTs*	*High*	
Decrease grade if	Serious limitation to study quality?	*No*		
	Important inconsistency?	*Yes - individual study effect sizes are inconsistent, I^2 = 78%*	*Mark down*	*Moderate*
	Uncertainty about directness?	*No*		
	Imprecise or sparse data?	*No*		
	High probability of reporting bias?	*No*		
Increase grade if	Strong evidence of association?	*No*		
	Evidence of a dose response gradient?	*No*		
	Plausible confounders would reduce effect?	*No*		***Moderate***

Testing for HCV antibodies: general strategy

GRADE assessment criteria		Assessment	GRADE score	GRADE running total
Type of evidence		*One RCT and 3 non-RCTs*	*High*	
Decrease grade if	Serious limitation to study quality?	*No*		
	Important inconsistency?	*Yes –individual study effect sizes are inconsistent, I^2 = 100%*	*Mark down*	*Moderate*
	Uncertainty about directness?	*No*		
	Imprecise or sparse data?	*Yes, wide confidence interval around effect size*	*Mark down*	*Low*
	High probability of reporting bias?	*No*		
Increase grade if	Strong evidence of association?	*No*		
	Evidence of a dose response gradient?	*No*		
	Plausible confounders would reduce effect?	*No*		***Low***

Testing for HCV antibodies: direct strategy

GRADE assessment criteria		Assessment	GRADE score	GRADE running total
Type of evidence		*4 RCTs, 6 non-RCTs*	*High*	
Decrease grade if	Serious limitation to study quality?	*No*		
	Important inconsistency?	*Yes - individual study effect sizes are inconsistent, I^2 = 94%*	*Mark down*	*Moderate*
	Uncertainty about directness?	*No*		
	Imprecise or sparse data?	*No*		
	High probability of reporting bias?	*No*		
Increase grade if	Strong evidence of association?	*No*		
	Evidence of a dose response gradient?	*No*		
	Plausible confounders would reduce effect?	*No*		***Moderate***

Testing HCV antibody positive: all strategies

GRADE assessment criteria		Assessment	GRADE score	GRADE running total
Type of evidence		*5 RCTs, and 9 non-RCTs. Sensitivity analysis showed little impact on effect size of including non-RCTs.*	*High*	
Decrease grade if	Serious limitation to study quality?	*No*		
	Important inconsistency?	*Yes - individual study effect sizes are inconsistent, I^2 = 76%*	*Mark down*	*Moderate*
	Uncertainty about directness?	*No*		
	Imprecise or sparse data?	*No*		
	High probability of reporting bias?	*No*		
Increase grade if	Strong evidence of association?	*No*		
	Evidence of a dose response gradient?	*No*		
	Plausible confounders would reduce effect?	*No*		***Moderate***

Testing HCV antibody positive: general strategy

GRADE assessment criteria		Assessment	GRADE score	GRADE running total
Type of evidence		*1 RCT and 3 non-RCTs. Sensitivity analysis showed little impact of including non-RCTs.*	*High*	
Decrease grade if	Serious limitation to study quality?	*No*		
	Important inconsistency?	*Yes - individual study effect sizes are inconsistent, I^2 = 58%*	*Mark down*	*Moderate*
	Uncertainty about directness?	*No*		
	Imprecise or sparse data?	*No*		
	High probability of reporting bias?	*No*		
Increase grade if	Strong evidence of association?	*No*		
	Evidence of a dose response gradient?	*No*		
	Plausible confounders would reduce effect?	*No*		***Moderate***

Testing HCV antibody positive: direct strategy

GRADE assessment criteria		Assessment	GRADE score	GRADE running total
Type of evidence		*4 RCTs and 6 non-RCTs. Sensitivity analysis showed little impact of including non-RCTs.*	*High*	
Decrease grade if	Serious limitation to study quality?	*No*		
	Important inconsistency?	*No*		
	Uncertainty about directness?	*Yes - individual study effect sizes are inconsistent, I^2 = 79%*	*Mark down*	*Moderate*
	Imprecise or sparse data?	*No*		
	High probability of reporting bias?	*No*		
Increase grade if	Strong evidence of association?	*No*		
	Evidence of a dose response gradient?	*No*		
	Plausible confounders would reduce effect?	*No*		***Moderate***

Referral to a HCV specialist: all strategies

GRADE assessment criteria		Assessment	GRADE score	GRADE running total
Type of evidence		*1 RCT (Inclusion of non-RCT evidence increased heterogeneity and effect size).*	*High*	
Decrease grade if	Serious limitation to study quality?	*No*		
	Important inconsistency?	*No*		
	Uncertainty about directness?	*No*		
	Imprecise or sparse data?	*Yes – only 1 RCT, due to results of sensitivity analysis*	*Mark down*	*Moderate*
	High probability of reporting bias?	*No*		
Increase grade if	Strong evidence of association?	*No*		
	Evidence of a dose response gradient?	*No*		
	Plausible confounders would reduce effect?	*No*		***Moderate***

Attendance at a HCV specialist: all strategies

GRADE assessment criteria		Assessment	GRADE score	GRADE running total
Type of evidence		*1 RCT (Inclusion of non-RCT evidence increased heterogeneity and effect size).*	*High*	
Decrease grade if	Serious limitation to study quality?	*No*		
	Important inconsistency?	*No*		
	Uncertainty about directness?	*No*		
	Imprecise or sparse data?	*Yes – only 1 RCT, due to results of sensitivity analysis*	*Mark down*	*Moderate*
	High probability of reporting bias?	*No*		
Increase grade if	Strong evidence of association?	*No*		
	Evidence of a dose response gradient?	*No*		
	Plausible confounders would reduce effect?	*No*		***Moderate***

Commenced HCV treatment: all strategies

GRADE assessment criteria		Assessment	GRADE score	GRADE running total
Type of evidence		*1 RCT and 2 observational studies. Inclusion of non-RCT evidence had minimal impact on effect size and heterogeneity.*	*High*	
Decrease grade if	Serious limitation to study quality?	*No*		
	Important inconsistency?	*No*		
	Uncertainty about directness?	*No*		
	Imprecise or sparse data?	*Yes – there was a very small number of events in both arms*	*Mark down*	*Moderate*
	High probability of reporting bias?	*No*		
Increase grade if	Strong evidence of association?	*No*		
	Evidence of a dose response gradient?	*No*		
	Plausible confounders would reduce effect?	*No*		***Moderate***

Sustained Virological Response (SVR): all strategies

GRADE assessment criteria		Assessment	GRADE score	GRADE running total
Type of evidence		*2 observational studies*	*Low*	
Decrease grade if	Serious limitation to study quality?	*No*		
	Important inconsistency?	*No*		
	Uncertainty about directness?	*No*		
	Imprecise or sparse data?	*Yes – there was a very small number of events in both arms*	*Mark down*	*Very low*
	High probability of reporting bias?	*No*		
Increase grade if	Strong evidence of association?	*No*		
	Evidence of a dose response gradient?	*No*		
	Plausible confounders would reduce effect?	*No*		***Very low***

All-cause mortality: all strategies

GRADE assessment criteria		Assessment	GRADE score	GRADE running total
Type of evidence		*1 RCT*	*High*	
Decrease grade if	Serious limitation to study quality?	*No*		
	Important inconsistency?	*No*		
	Uncertainty about directness?	*Yes – six months follow-up is inadequate to compare mortality in the two arms*	*Mark down*	*Moderate*
	Imprecise or sparse data?	*Yes – only 1 study, small n*	*Mark down*	*Low*
	High probability of reporting bias?	*No*		
Increase grade if	Strong evidence of association?	*No*		
	Evidence of a dose response gradient?	*No*		
	Plausible confounders would reduce effect?	*No*		***Low***

Appendix 6: Newcastle-Ottawa Scale

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE FOR COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community *****
   b) somewhat representative of the average _____ in the community *****
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort
2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort *****
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort
3) Ascertainment of exposure
   a) secure record (eg surgical records) *****
   b) structured interview *
   c) written self report
   d) no description
4) Demonstration that outcome of interest was not present at start of study
   a) yes *****
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor) *****
   b) study controls for any additional factor ***** (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment *****
   b) record linkage *****
   c) self report
   d) no description
2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) *****
   b) no
3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for *****
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) *****
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

Appendix 7: GRADE approach to assessing the quality of evidence across studies

<table>
<tr><th>Quality of Evidence (summary score)</th><th>Study Design</th><th>Downgrading Factors</th><th>Upgrading Factors</th></tr>
<tr><td>High (4) =Further research is very unlikely to change our confidence in the estimate of effect.</td><td>Randomized trials or valid accuracy studies for diagnostic tests begin with a score of High (4)</td><td rowspan="4">Study Limitations:
-1 Serious
-2 Very serious

Consistency:
-1 Serious
-2 Very serious

Directness:
-1 Serious
-2 Very serious

Precision:
-1 Serious
-2 Very serious

Publication Bias:
-1 Serious
-2 Very serious</td><td rowspan="4">Large effect
+1 Large
+2 Very large

Plausible confounding would change the effect
+1

Dose-response gradient
+1 if Present</td></tr>
<tr><td>Moderate (3) = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</td><td></td></tr>
<tr><td>Low (2) = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</td><td>Observational studies or indirect accuracy studies for diagnostic tests begin with a score of low (2).</td></tr>
<tr><td>Very low (1) = Any estimate of effect is very uncertain.</td><td></td></tr>
</table>