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TITLE PAGE

Interventions to enhance testing and linkage to treatment for hepatitis C infection: a systematic review and meta-analysis

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Abstract

Background: The availability of simple and effective direct-acting antiviral (DAA) therapies has improved management of hepatitis C virus (HCV) infection. Despite the goal set by the World Health Organization to eliminate HCV as a public health threat, HCV testing and treatment remains low. To achieve these targets, evidence-based interventions are needed to address the barriers to care for people with HCV infection. We aimed to assess the efficacy of interventions to improve HCV antibody testing, HCV RNA testing, linkage to care, and treatment initiation.

Methods: In this systematic review and meta-analysis, we searched bibliographic databases and conference abstracts for studies assessing interventions to improve the following study outcomes to July 21, 2020: HCV antibody testing, RNA testing, linkage to care, and treatment initiation. We included randomised and non-randomised studies assessing non-pharmaceutical interventions that included a comparator arm. Studies were excluded if they enrolled only paediatric populations (<18 years old) or if the intervention was conducted in a different healthcare setting than the control or comparator. Data were extracted from the records identified and meta-analysis was used to pool the effect of interventions on study outcomes. This study was registered in PROSPERO (CRD42020178035)

Findings: Of 15,342 unique records, 142 studies assessing an intervention to improve HCV testing, linkage to care and treatment initiation were included. These included 47 randomised trials and 102 non-randomised studies. Medical chart reminders, provider education, and point-of-care antibody testing showed improvements across three or more study outcomes. Interventions which simplified HCV testing including dried blood spot testing, point-of-care antibody testing, reflex RNA testing, and opt-out screening improved testing outcomes. Enhanced patient and provider support through patient education, patient navigation, provider

care coordination, and provider education also improved testing outcomes. Integrated care and patient navigation improved linkage to care and treatment uptake.

Interpretation: A host of interventions to improve HCV care were identified which address several key barriers to HCV care. New models of HCV care must be designed and implemented to address the barriers faced by the population of interest. Further high-quality research, including rigorously designed randomised studies, are still needed in key populations.

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Introduction

Hepatitis C virus (HCV) infection remains a public health threat, with an estimated 58 million people infected worldwide.[1] Direct-acting antiviral (DAA) therapies have improved HCV management with population-level impacts on liver disease burden.[2-5] Despite the World Health Organization goal to eliminate HCV as a public health threat,[6] HCV testing and treatment remains low.[1] Implementing interventions to enhance HCV testing, linkage to care, and treatment is critical to achieve HCV elimination.

Previous systematic reviews evaluating interventions to enhance HCV testing and treatment, were limited by the small numbers of studies identified, a lack of studies performed in the DAA era[7-10], and have been restricted to specific priority populations (e.g. people who inject drugs and people in prison).[7,8] A considerable amount of research has since been performed in the DAA era, including a larger number of randomised studies, enhancing data quality.

To address this gap in the literature, we conducted a systematic review to evaluate the effect of any interventions to enhance testing, linkage to care, and treatment initiation for HCV infection in all populations.

Methods

The systematic review and meta-analysis is reported in accordance with PRISMA[11], MOOSE[12], and GATHER[13]. The protocol is registered with PROSPERO (CRD42020178035).

Eligibility criteria

Studies meeting the following criteria were included: study population included people at risk of HCV infection (testing outcomes) or those with HCV infection (linkage to care and treatment initiation); implemented an intervention; included a comparator or control; and reported one or more of the following outcomes: HCV antibody testing uptake, HCV RNA testing uptake, linkage to HCV care, and HCV DAA treatment initiation. Data were also collected for treatment outcome measures including adherence to treatment, treatment completion, sustained virologic response, and post-treatment follow-up as described in the protocol. These data will be published separately to describe interventions to improve HCV treatment outcomes. Randomised controlled trials and controlled non-randomised studies were included. Non-randomised studies included those with a historical control comparing the study outcome before and after the implementation of an intervention (e.g., historically controlled studies, interrupted time series studies), those where a consistent population was observed before and after the implementation of the intervention (e.g., cohort studies, controlled before and after studies), and those with a non-randomised control population (e.g., non-randomised controlled studies, non-randomised cluster controlled studies).

Studies were excluded if they enrolled only paediatric populations (<18 years old), did not report sufficient data for any study outcome, assessed a pharmaceutical intervention (e.g.,

comparing two different treatment regimens), or if the intervention was conducted in a different healthcare setting than the control or comparator population.

Information sources and search

We conducted a systematic search of the scientific peer-reviewed literature indexed in five databases: MEDLINE (Pubmed), Scopus, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), and PsycINFO. Abstracts of key conferences were searched, including the International Liver Congress, Liver Meeting, Conference on Retroviruses and Opportunistic Infections, and International Conference on Health and Hepatitis Care in Substance Users. Reference lists of the articles included in the analysis, and relevant review articles were hand-searched for relevant citations. The initial search was conducted on December 19, 2019 with no time restriction for searches. The search was updated on July 21, 2020. Combinations of search terms relating to HCV, testing and treatment interventions, and outcomes were used (Appendix p2).

Study selection

Records identified through the search strategy were imported into Endnote X8 (Thomson Reuters, New York, NY, USA), duplicates removed, and imported to Covidence for screening. Titles, abstracts, and full text were screened in Covidence for eligibility by two separate reviewers with conflicts resolved by a third (EBC, JG, BH, ADM, SB, AW, AC, and BMV). In the case of multiple publications of one study, the publication with the most up-to-date data was included, with other publications excluded but retained for supplementing incomplete data, if necessary.

Data collection process and data items

All data were extracted by one reviewer and double-checked by a second (EBC, JG, BH, SB, AW, AC, and BMV). Where disagreements in the extracted data were found, the conflict was reconciled by a third reviewer. Data were extracted into a pre-piloted and standardised data extraction form (Microsoft Excel for Office 365, Redmond, WA, USA). Data extracted included study and intervention characteristics, participant characteristics, and outcomes of the interventions (Appendix p39-43). Data collected for HCV antibody testing were the number who received HCV antibody testing (n) out of the number eligible for testing (N). Data collected for HCV RNA testing were the number who received HCV RNA testing (n) out of the number eligible for HCV RNA testing (N). Data collected for linkage to care were the number who attended a follow-up appointment with a clinician (n) out of the number who were HCV RNA positive (N). Data collected for HCV treatment initiation were the number who initiated HCV treatment (n) out of the number eligible for treatment (N). All first and senior study authors were contacted by email to clarify study details and to obtain additional data. Two reminder emails were sent to study authors who did not respond to the initial request.

Interventions assessed in each study were extracted to determine all intervention components. Intervention components were categorised into an inductively generated list of discrete intervention descriptors and extracted (Appendix p38). Where the control or comparator arm differed from standard of care for that setting, the individual components of the comparator treatment were extracted. In studies with multiple intervention components included in the intervention arm, the principal component was determined. Where a principal component could not be assigned due to the complexity of the intervention, the study was categorised as a “Multiple component intervention”. Where interventions were successively implemented in a phased or quality improvement initiative, each phase was extracted compared to the

previous phase where possible. An overarching comparison of the final phase which included all intervention components to the initial phase was also conducted where possible. Such combined interventions were extracted as a "Phased/quality improvement initiative". All intervention extractions including the intervention components present in each study as well as the principal intervention were extracted in duplicate with any discrepancies resolved by a third reviewer (EBC, AW, JG, and BH).

Risk of bias in individual studies

Risk of bias was assessed for randomised controlled trials (Cochrane RoB 2 tool[14]) and non-randomised studies (ROBINS-I tool[15]). If a single study reported outcomes at multiple stages of the care cascade, risk of bias was assessed for each stage independently. Studies were ranked as having low risk, some concerns, or high risk of bias across five domains for randomised studies (RoB 2), and the overall risk of bias was derived. Studies were ranked as having low, moderate, serious, or critical risk of bias across seven domains for non-randomised studies (ROBINS-I). Risk of bias assessment was conducted in duplicate with any discrepancies discussed with a third reviewer (CEF, RR, AW, AC, and GF).

Synthesis of results

The primary outcomes of interest for this review were HCV antibody testing uptake, HCV RNA testing uptake, linkage to HCV care, and HCV DAA treatment initiation. The proportion of people with each outcome of interest was assessed and corresponding odds ratios (OR), standard errors, and 95% confidence intervals were calculated for the association between receiving the intervention and the study outcome.

Random effects meta-analysis was used to synthesise the pooled outcome measure estimates. Principal intervention components with more than one assessment were eligible for meta-analysis. Heterogeneity across studies was measured with the I^2 statistic, with an I^2 of less than 25%, 25-75%, and more than 75% considered as low, moderate, and high heterogeneity respectively. Stratified meta-analyses by randomisation status (randomised and non-randomised designs) and treatment type (treatment initiation outcome only; DAA and interferon-based treatment) were conducted to assess the impact of non-randomised study designs on the study outcomes.

Logit transformed outcome estimates were used in all meta-analyses, while the estimates were back-transformed for reporting. A fixed continuity correction of 0.5 was applied where there was a zero cell in calculating ORs. Two-sided p values of less than 0.05 were deemed to be statistically significant. All analyses were done with Stata version 14.0.

Role of the funding source

The funders of the authors had no role in the design, data collection, analysis, or interpretation of this work. All authors had independent access to the study data and were responsible for the decision to submit for publication.

Results

A total of 33,942 records from bibliographic databases and 46 records from other sources were identified resulting in 15,342 unique records. Of these, 142 unique records were included (Figure 1; 109 journal articles, 33 conference abstracts). These records reported on 148 unique studies with 213 total assessments of study outcomes (one for each intervention arm for each study outcome assessed).

Description of studies

Table 1 summarises the characteristics of the included studies, including 47 randomised controlled trials and 102 non-randomised studies. The most common study designs were historically controlled studies (K=74), randomised controlled trials (K=30), cluster randomised trials (K=17), non-randomised controlled trials (K=14), and cohort studies (K=9).

There were 87 studies (100 assessments) contributing data to HCV antibody testing (randomised trials, K=31; non-randomised studies, K=56), 24 studies (27 assessments) contributing data to HCV RNA testing (randomised controlled trials, K=4; non-randomised studies, K=20), 37 studies (42 assessments) contributing data to linkage to care (randomised controlled trials, K=12; non-randomised studies, K=25), and 41 studies (44 assessments) contributing data to HCV treatment initiation (randomised controlled trials, K=13; non-randomised studies, K=28).

Risk of Bias

Among the 37 assessments of interventions to improve antibody testing in randomised studies, the risk of bias was assessed as high, some concerns, and low for five (14%), 22 (59%), and 10 (27%) assessments, respectively. Among the four assessments of interventions

to improve RNA testing in randomised studies, the risk of bias was assessed as some concerns for all four (100%) of assessments. Among the 13 assessments of interventions to improve linkage to HCV care in randomised studies, the risk of bias was assessed as some concerns in nine (69%) assessments and low for four (31%) assessments. Among the 15 assessments of interventions to improve HCV DAA treatment initiation in randomised studies, the risk of bias was assessed as high, some concerns, and low for four (27%), seven (47%), and four (27%) assessments, respectively. The domain most often associated with a high risk of bias was the randomisation process (Appendix p57-68).

The risk of bias among the non-randomised studies was critical for 95% (60/63), 92% (21/23, 93% (27/29), and 82% (24/29) for studies investigating interventions to enhance HCV antibody testing, HCV RNA testing, linkage to care, and HCV treatment initiation, respectively. No assessment of any outcome had a low risk of bias. The confounding domain most often associated with a critical risk of bias due to no adjustment for confounding (Appendix p57-68).

Impact of interventions on HCV antibody testing

Among the 26 principal intervention components assessed, 15 interventions had sufficient data to be pooled (>1 assessment per principal intervention component). The following interventions improved HCV antibody testing: point-of-care antibody testing (definitions for all interventions are provided in Supplementary Table 7; K=4; OR 21.05 95% CI 6.98-63.52; I^2=92.6%); opt-out screening (K=3; OR 18.97, 95% CI 1.91-188.61; I^2=99.1%); patient reminders for testing/treatment (K=9; OR 9.76, 95% CI 3.99-23.88; I^2=99.9%); medical chart reminders (K=25; OR 6.75, 95% CI 4.41-10.34; I^2=99.8%); patient education (K=6; OR 4.18, 95% CI 1.25-13.96; I^2=95.3%); provider care coordination (K=2; OR 3.68, 95% CI 2.12-

6.38; I^2=66.9%); memory practice (a psychological intervention seeking to improve client recall of recently learned information; K=2; OR 2.45, 95% CI 1.50-4.01; I^2=0%); dried-blood-spot testing (K=3; OR 2.42, 95% CI 1.45-4.02; I^2=94.7%); and provider education (K=11; OR1.78, 95% CI 1.49-2.14; I^2=95.9; Table 2, Figure 2, and Supplementary figure 1). On-site oral swab collection, financial incentives to providers, direct solicitation of patients, implementation of systematic testing, risk-based screening tool, nurse-led care, pharmacist led treatment, and directly observed therapy demonstrated a positive effect on HCV antibody testing in single studies.

In studies with randomised designs, patient reminders for testing/treatment (K=4; OR 10.07, 95% CI 3.27-30.97, I^2=99.8%), medical chart reminders (K=3; OR 8.16, 95% CI 3.75-17.77, I^2=98.4%), point-of-care antibody testing (K=3; OR 25.08, 95% CI 4.23-148.64, I^2=93.0%), memory practice (K=2, OR 2.45, 95% CI 1.50-4.01, I^2=0%), and dried-blood-spot testing (K=2; OR 2.25, 95% CI 1.17-4.33, I^2=97.3%) increased HCV antibody testing (Appendix p50).

Impact of interventions on HCV RNA testing

Among the 12 principal intervention components assessed, five interventions had sufficient data to be pooled. The following interventions improved HCV RNA testing: medical chart reminders (K=4; OR 3.87, 95% CI 1.68-8.95, I^2=90.4%); and reflex HCV RNA testing (HCV RNA testing on the same sample collected for positive HCV antibody testing; K=3; OR 9.31, 95% CI 2.31-37.48, I^2=97.4%; Table 2, Figure 3, and Supplementary figure 1). Provider education and provider care coordination interventions demonstrated a positive effect on HCV RNA testing in single studies.

In the subgroup of studies with randomised designs, there were no interventions eligible for meta-analysis.

Impact of interventions on linkage to care

Among the 16 unique principal intervention components, nine interventions had sufficient data to be pooled. The following interventions improved linkage to care: medical chart reminders (K=4; OR 2.81, 95% CI 1.66-4.78, I^2=84.8%); provider education (K=2; OR 1.54, 95% CI 1.12-2.13, I^2=9.5%); integrated care (K=4; OR 3.82, 95% CI 1.64-8.89, I^2=62.1%); patient navigation or care coordination (K=4; OR 3.25, 95% CI 2.31-4.57, I^2=0%); and point-of-care antibody testing (K=3; OR 1.70, 95% CI 1.35-2.16, I^2=0%; Table 2, Figure 4, and Supplementary figure 1). Dried-blood-spot testing, reflex RNA testing, and on-site oral swab collection demonstrated a positive effect on linkage to HCV care in single studies.

In studies with randomised designs, patient navigation or care coordination (K=3; OR 3.10, 95% CI 2.05-4.69, I^2=0%) and point-of-care antibody testing (K=3; OR 1.70, 95% CI 1.35-2.16, I^2=0%) demonstrated an improvement in linkage to HCV care (Appendix p53).

Impact of interventions on HCV treatment initiation

Among the 16 unique principal intervention components to improve HCV DAA treatment uptake, five interventions had sufficient data to be pooled. The following interventions improved HCV DAA treatment initiation: integrated care (K=3; OR 8.53, 95% CI 1.08-67.24; I^2=88.8%); and patient navigation or care coordination (K=5; OR 2.48, 95% CI 1.26-4.88; I^2=78.4%; Table 2, Figure 5, and Supplementary figure 1). Medical chart reminders, point-of-care antibody testing, broadened testing/treatment criteria, motivational

interviewing, and nurse-led care demonstrated a positive effect on HCV DAA treatment initiation in a single study.

In studies of interferon-based treatment, psychological therapy was the only intervention with sufficient data for meta-analyses and demonstrated an improvement in treatment initiation (K=3; OR 2.20, 95% CI 1.47-3.28; Appendix p48)

In studies with randomised designs, no intervention to date showed evidence of improvement in DAA treatment initiation (Appendix p55).

Discussion

This systematic review identified a range of interventions to enhance HCV testing, linkage to care, and treatment initiation. Interventions effective at improving HCV care included those simplifying HCV testing, enhancing patient engagement with care, and improving provider engagement. Interventions were directed at the level of the patient, provider, or health system, highlighting the role of individual, provider, and contextual factors in shaping health care access, including how they interact to present or impede opportunities for care. The interventions identified have varied mechanisms of action supporting the identification and assertion of candidacy for HCV care[16] by addressing barriers or enhancing facilitators to care faced by affected populations. In 2016, the WHO released a Global Health Sector Strategy on Viral Hepatitis that proposed the first-ever global hepatitis targets with aims to eliminate HCV as a public health threat by 2030.[6] To achieve this target for HCV, interventions such as those identified within this systematic review are needed to target gaps in care and barriers to care at all levels of the health system.

Medical chart reminders, provider education, and point-of-care antibody testing interventions demonstrated efficacy across three or more stages of the HCV care cascade. Medical chart reminders improved HCV antibody testing, RNA testing, linkage to HCV care, and a single study demonstrated a positive impact on treatment uptake. This is consistent with the effect of medical reminders to improve screening for HIV, HBV, colorectal cancer, and diabetes.[17-21] These reminders act by removing provider-level barriers caused by acts of omission that can occur from an overload of information for clinicians, competing medical priorities, or an outdated knowledge of testing guidelines.[22-24] Given the effect of medical reminders on all stages of the care cascade and their relatively simple implementation, further work is required

to embed and optimise this strategy into health systems to improve outcomes for HCV infection.

Provider education was shown to have a positive impact on HCV antibody testing, HCV RNA testing, and linkage to HCV care, although data for HCV RNA testing (two studies) and linkage to HCV care (one study) derive from few studies and warrant further study. The observed impact is consistent with the effect of provider education on enhancing HIV care[25-27] and addresses many of the same barriers.[28] Provider education reduces provider-level barriers to HCV care by improving competency and enhancing provider motivation to engage in HCV care.[29,30] Further work is needed to expand education and training of HCV providers, particularly among general practitioners as HCV treatment restrictions are removed globally, and to better understand the impact of provider education on later stages such as linkage to HCV care.[31]

Point-of-care antibody testing was effective at increasing HCV antibody testing, linkage to care, and a single study demonstrated a positive impact on treatment uptake, consistent with the effects of point-of-care HIV testing .[32-34] Point-of-care testing reduces loss to follow-up by enabling testing to occur on-site, decreases the number of visits to receive a diagnosis, and reduces the need for referral to off-site pathologists.[35] Point-of-care testing eliminates venepuncture, addressing a key barrier to testing among people who inject drugs who often have poor venous access and prefer finger-stick testing to venepuncture.[22,29,36] A new point-of-care HCV RNA test has recently been approved, the Xpert HCV Viral Load Fingerstick assay (Cepheid, Sunnyvale, CA, USA), detecting active infection in an hour with good technical accuracy[35,37] providing the opportunity for diagnosis and treatment in a single visit. Interventions facilitating same-day treatment initiation are likely to have a large impact on

treatment initiation.[35,38,39] Further data evaluating the impact of point-of-care HCV RNA testing on the HCV care cascade are needed.

Interventions simplifying HCV testing had positive effects on HCV antibody and RNA testing. In addition to point-of-care HCV antibody testing, several interventions simplifying testing improved HCV care. Dried-blood-spot testing improved HCV antibody testing in three studies, addressing many of the same barriers as point-of-care testing, including the ability to perform testing on-site and avoiding the need for venepuncture. One limitation of dried-blood-spot testing compared to point of care testing is that same-visit diagnosis is not possible due to the need for testing at a central laboratory. Further work is needed to identify interventions that can be coupled with dried-blood-spot testing to facilitate linkage to treatment following testing. Despite this limitation, dried-blood-spot testing remains an important intervention for improving the reach of testing and engaging people in care who might not otherwise have been engaged through conventional models.

Reflex RNA and opt-out screening are two interventions simplifying testing at the systems level and were effective at enhancing testing. Opt-out testing was shown to improve antibody testing, consistent with opt-out testing for HIV and other sexually transmitted infections and is part of the guidance for HIV testing provided by the WHO.[28,40] Even with opt-out antibody testing there remains a need for confirmatory HCV RNA testing among people who are HCV antibody positive, often requiring people to reattend a health service which can lead to loss to follow-up.[41,42] Reflex RNA testing from the same sample used for HCV antibody testing was shown in this review to improve HCV RNA testing. Reflex RNA testing simplifies testing by reducing the number of provider visits and minimises loss to follow-up.[23,43,44] This intervention has become standard practice in the UK with guidelines recommending its use

for all antibody positive tests.[45] Challenges for implementing reflex RNA testing include the availability of laboratory platforms with automated processes for HCV antibody and RNA testing on the same sample, including minimising potential for contamination between samples. Further work is needed to address laboratory workflow barriers to enable reflex HCV RNA testing to be incorporated more broadly into standard practice.

Several studies implemented interventions improving patient engagement in care. Case-finding of people who have never been tested for HCV infection is important to ensure that testing priorities are met, including one-time age-based testing recommendations in some countries.[46] One intervention to initiate patient engagement in HCV care was patient reminders for testing or treatment. By informing patients that they were eligible or recommended for treatment, this intervention was effective at engaging people in HCV antibody testing consistent with the impact of reminders for sexually transmitted infection testing.[47]

One intervention type to increase patient engagement with ongoing HCV care was patient navigation or care coordination. Patient navigation can help to remove barriers caused by fragmented service provision and difficulties in obtaining the necessary referrals.[22,23] Patient navigation was shown to improve linkage to HCV care (three studies) and DAA treatment initiation (four studies) consistent with patient navigation in the context of other chronic diseases including cancer, diabetes, and HIV.[48] This intervention was shown to be of utility in populations who often experience disadvantage in the healthcare system such as people who use drugs and people who are socioeconomically disadvantaged. Such populations often have irregular contact with health services and often experience discrimination in these settings, impacting their ability to progress through HCV care.[23,49] Patient education regarding HCV

infection and HCV treatment was also effective at improving HCV antibody testing uptake. The positive impact of education on HCV testing in this review is consistent with educational interventions to enhance HIV testing[50] and is regularly implemented to improve engagement in care for other chronic diseases.[51,52] In this review, studies of patient education were infrequently implemented in isolation and education was rarely the principal component in multicomponent studies and as such, there remains insufficient data to assess the impact of patient education on the other study outcomes.

A third group of interventions which demonstrated an impact on HCV care were interventions which sought to increase and simplify provider engagement in HCV care. Providers are tasked with caring for and managing a diverse range of populations in diverse settings. Additional support has the potential to improve patient outcomes at all stages of the care cascade. In addition to medical chart reminders and provider education, provider care coordination provides holistic support to providers by identifying and addressing context specific barriers to HCV care, encouraging adherence to HCV guidelines, and providing education to clinicians as needed. This flexible approach to improving HCV care was effective at improving HCV antibody testing (two studies) and HCV RNA testing (one study) although data are derived from few studies and further research is needed to confirm this impact in diverse settings and populations. The impact of studies in this review are consistent with findings in the drug and alcohol and mental health fields demonstrating the positive impact of such coordinators or clinical champions on improving uptake of health interventions, overcoming systemic barriers, and enhancing staff engagement and motivation.[53]

Integrated care increased linkage to HCV care, DAA treatment initiation. The impact observed is consistent with evidence demonstrating the effect of integrated care on improving HIV and other infectious and chronic disease care.[54-58] Integration of HCV testing/treatment into other settings, such as mental health or drug treatment services, addresses barriers at several levels. At the patient-level, integration addresses barriers relating to the navigation and permeability of health services,[16] financial barriers, and barriers caused by limited resources and time, thereby improving ongoing engagement with HCV care.[23] By collocating HCV care within a service where patients are already comfortable accessing care, integrated care reduces the barriers caused by the fragmentation of health services and potential stigma and discrimination faced when accessing care outside of trusted services.[59,60] This reduced fragmentation of health services also addresses provider-level barriers to HCV care by limiting the need for referral and coordination with external health services. Given the move towards more population-centric models of care and integrated strategies for HCV, HIV and STIs by WHO[1], further work should be done to improve integration of care for HCV infection and other diseases.

There were also several studies which implemented a complex intervention combining several interventions. Similarly, phased or quality improvement initiatives sequentially implemented interventions to address remaining barriers to care. While meta-analyses of these interventions must be interpreted with caution due to the heterogeneous nature of these interventions, it demonstrated that multifaceted interventions can be highly effective at improving all stages of the HCV care cascade.

The feasibility and impact of interventions are likely to vary by population and setting based on the availability of resources and the differential impact of interventions between settings

and populations. Cost and cost-effectiveness are of particular importance in resource-limited settings and may limit the feasibility of some interventions in low- and middle-income countries. With the majority of the burden of HCV occurring in low- and middle-income countries, research is needed to determine the impact and feasibility of interventions in these settings.

There are several limitations to this review. First, many studies included in the testing and linkage to care outcomes occurred in the era of interferon-based HCV treatment. While the change in efficacy and tolerability may have had an impact on these outcomes, strategies effective in this past era are likely to still be relevant in the new era of DAA therapy. For treatment initiation, studies were restricted to only those conduced in the DAA era given that the efficacy and tolerability may have had a considerable impact on patient and provider willingness to initiate treatment. Unfortunately, due to the complexity of the global roll out of DAA therapies, it was not possible to determine what treatments were available to the study population at the time of the study for studies which investigated testing and linkage to care but not treatment. Second, while there was greater representation of low-and middle-income countries compared to previous reviews, the majority of studies were conducted in high-income countries and may not be generalisable to resource-limited settings. Third, many interventions included several components resulting in insufficient power to assess the individual impact of interventions that are frequently implemented as part of complex interventions (such as peer-based support). Fourth, the comparator treatments were often heterogeneous and poorly described which could have had an impact on the effectiveness of an intervention. The risk of publication bias must also be considered especially in the context of non-randomised observational studies where ineffective interventions may not have been published. Due to the small number of studies included for most individual interventions it

was not possible to assess whether there was evidence of publication bias. Further, the risk of bias was high, particularly in non-randomised studies, most commonly due to the lack of adjustment for confounders. The absence of adjustment for confounders in the majority of studies is a major limitation and must be considered when assessing the outcomes of these studies. Given how common critical risk of bias was in non-randomised studies, sensitivity analyses among only those at low risk of bias was not possible. Lastly, although this review identified a greater number of randomised studies compared to previous reviews, the majority of studies remain non-randomised with little or no adjustment for confounding, reducing the quality of the data. Combining randomised studies and non-randomised studies increases the potential for selection bias, particularly given the high risk of bias across studies likely contributing to the high heterogeneity observed in this review. Sensitivity analyses among only randomised studies showed similar results to the combined analyses for several of the interventions, particularly for antibody testing and linkage to HCV care; however, several of the interventions presented in this review lack evidence from randomised trials and warrant further study.

Our review demonstrates a diverse range of interventions to improve HCV testing, linkage to care, and DAA treatment initiation. The use and implementation of these interventions to improve models of HCV care will depend on the unique context-specific barriers faced in varied populations, settings, and existing gaps in the care cascade. This is particularly relevant now given the challenges posed by the COVID-19 pandemic that has seen considerable disruptions in HCV care globally.[61,62] Interventions which overcome the barriers to care caused by limits on face-to-face interactions such as telehealth, integration of COVID-19 and HCV care[63], self-testing, and patient navigation will become increasingly important.[61,64] More broadly, many of the interventions identified are simple and inexpensive,

increasing their utility in routine clinical care. Simplified testing modalities which improve the patient experience were highly effective at increasing testing, while increased patient and provider support were shown to improve care across all outcomes. Interventions addressing setting- and population-specific barriers are likely to be most effective at improving HCV care. With the high efficacy of DAA therapies, simplifying care and enabling patients to progress to treatment initiation is critical. Further high-quality research, including rigorously designed randomised studies, are still needed. Further work is needed to identify interventions which are most efficacious and cost-effective in key populations and settings to achieve the greatest global impact. With the broad implementation of effective interventions, considerable progress towards global HCV elimination can be achieved.

Contributors

Evan B Cunningham (EBC) and Jason Grebely (JG) designed and proposed the study with contributions in study design from Gregory J Dore (GJD), Behzad Hajarizadeh (BH), Alison D Marshall (ADM), Matthew Hickman (MH), Peter Vickerman (PV), Sahar Bajis (SB), Clare French (CEF), and Rachel Roche (RR). Screening, review, data extraction and verification was conducted by EBC, JG, BH, ADM, SB, CEF, RR, Alice Wheeler (AW), Anna Conway (AC), Guillaume Fontaine (GF), and Braulio M Valencia (BMV). Data analysis was conducted by EBC. Justin Presseau (JP), John Ward (JW), Louisa Degenhardt (LD), PV, MH, GF, GJD, BH, EBC and JG assisted in interpretation of the study results. EBC and JG drafted the first iteration of the manuscript. All authors made substantial contributions to the critical review, editing, and revision of the manuscript. All authors approved the final version of the manuscript.

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Declaration of interests

JG is a consultant/advisor and has received research grants from AbbVie, Camurus, Cepheid, Gilead Sciences, Hologic, Indivor, and Merck/MSD and has received honoraria from AbbVie, Cepheid, Gilead Sciences, and Merck. GJD is a consultant/advisor and has received research grants from Abbvie, Abbot Diagnostics, Gilead Sciences, Bristol Myers Squibb, Cepheid, GlaxoSmithKline, Merck, Janssen and Roche. JWW is supported by The Task Force for Global Health which receives funds for the general support of the Coalition for Global Hepatitis Elimination from Abbott, Gilead, AbbVie, Merck, Siemens, Cepheid, Roche, Pharco, Zydus-Cadila, governmental agencies and philanthropic organizations. MH has received unrestricted honoraria and travel expenses from MSD and Gilead unrelated to this project. PV has received research grants from Gilead Sciences and is in receipt of grants from the UK National Institute of Health Research. AC, ADM, AW, BMV, BH, CEF, EBC,

GF, JP, LD, RR, and SB had no conflict of interest to declare. No input into this work was provided by any of the above listed organisations or institutions.

Data sharing statement

The majority of the data collected for this study are publicly available. Additional data obtained from authors, coding, data dictionary, or study materials are available upon request to the corresponding author.

Tables and figures

Table 1. Summary of included study characteristics

	HCV antibody testing (K=87)		HCV RNA testing (K=25)		Linkage to care (K=37)		Treatment initiation (K=41)	
	K (%)	**n**	**K (%)**	**n**	**K (%)**	**n**	**K (%)**	**n**
Study design								
Randomised controlled trial	17 (20)	58,634	1 (4)	12,386	9 (24)	2,402	9 (22)	2,097
Cluster randomised controlled trial	14 (16)	192,999	3 (12)	401	3 (8)	5,220	4 (10)	5,654
Non-randomised controlled trial	8 (9)	296,051	2 (8)	941	4 (11)	608	4 (10)	661
Historically controlled study	44 (51)	1,466,279	16 (64)	48,552	17 (46)	16,408	16 (39)	7,711
Cohort study	0 (0)	0	2 (8)	885	3 (8)	1,310	6 (15)	75,312
Controlled before and after study	3 (3)	132,414	0 (0)	0	1 (3)	571	1 (2)	571
Interrupted time series study	1 (1)	393,517	0 (0)	0	0 (0)	0	0 (0)	0
Non-randomised cluster controlled study	0 (0)	0	1 (4)	1,671	0 (0)	0	1 (2)	1,228
Study setting								
Primary care/general practice	43 (49)	1,234,190	10 (40)	17,906	10 (27)	6,579	5 (12)	44,520
Hospital outpatient/tertiary clinic	6 (7)	76,500	1 (4)	4,002	5 (14)	7,785	16 (39)	6,646
Drug treatment	5 (6)	3,615	1 (4)	257	5 (14)	1,995	6 (15)	2,334
Population-based	4 (5)	709,286	3 (12)	12,659	7 (19)	7,394	4 (10)	36,948
Emergency department	4 (5)	72,051	2 (8)	1,372	1 (3)	295	0 (0)	0
Hospital (inpatient)	3 (3)	211,965	1 (4)	702	1 (3)	93	0 (0)	0
Prison	7 (8)	124,122	4 (16)	16,653	0 (0)	0	2 (5)	281
Other	15 (17)	108,165	3 (12)	11,285	8 (22)	2,378	8 (20)	2,505
Population								
General population	10 (11)	854,606	7 (28)	14,535	13 (35)	15,334	14 (34)	41,376
Birth cohort	35 (40)	731,507	4 (16)	15,834	3 (8)	1,243	0 (0)	0
People receiving OAT	5 (6)	4,540	1 (4)	114	2 (5)	408	2 (5)	478
People in prison	7 (8)	124,122	4 (16)	16,653	0 (0)	0	2 (5)	281

People who inject drugs	6 (7)	37,393	2 (8)	1,753	4 (11)	6,179	6 (15)	7,554
People who use drugs	1 (1)	162	1 (4)	107	3 (8)	118	2 (5)	200
People attending drug/alcohol service	2 (2)	375	2 (8)	9,764	1 (3)	1,008	2 (5)	1,345
Mixed	2 (2)	12,402	0 (0)	0	2 (5)	472	3 (7)	551
Other	19 (22)	774,787	4 (16)	6,076	9 (24)	1,757	10 (24)	41,449
Number of Centres								
Single-centre	28 (32)	507,349	7 (28)	28,241	13 (35)	2,622	17 (41)	3,665
Multicentre	59 (68)	2,032,544	18 (72)	36,595	24 (65)	23,897	24 (59)	89,569
Country income status			0 (0)					
Low income	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0
Lower-middle income	0 (0)	0	0 (0)	0	1 (3)	5,118	2 (5)	6,331
Upper-middle income	0 (0)	0	2 (8)	11,887	1 (3)	7,410	2 (5)	2,688
High income	87 (100)	2,539,893	23 (92)	52,949	35 (95)	13,991	37 (90)	84,215

K represents the number of studies, N represents the number of patients

Table 2. Summary of primary intervention components

	Antibody testing			RNA testing			Linkage to care			Treatment initiation		
Intervention	No of studies (RCT/ NRS)	Odds ratio (95% CI)	I^2	No of studies (RCT/ NRS)	Odds ratio (95% CI)	I^2	No of studies (RCT/ NRS)	Odds ratio (95% CI)	I^2	No of studies (RCT/ NRS)	Odds ratio (95% CI)	I^2
Medical chart reminders	25 (3/22)	6.75 (4.41-10.34)	99.8	4 (0/4)	3.87 (1.68-8.95)	90.4	4 (0/4)	2.81 (1.66-4.78)	84.8	1 (0/1)	1.90 (1.42-2.53)	
Provider education	11 (0/11)	1.78 (1.49-2.14)	95.9	1 (0/1)	17.95 (10.45-30.85)		2 (0/2)	1.54 (1.12-2.13)	9.5	2 (0/2)	2.03 (0.70-5.87)	97.0
Integrated care	2 (1/1)	5.52 (0.14-223.76)					4 (1/3)	3.82 (1.64-8.89)	62.1	3 (1/2)	8.53 (1.08-67.24)	88.8
Point-of-care antibody testing	4 (3/1)	21.05 (6.98-63.52)	92.6	1 (0/1)	0.25 (0.03-1.96)		3 (3/0)	1.70 (1.35-2.16)	0.0	1 (1/0)	2.10 (1.51-2.92)	
Point-of-care RNA testing				2 (0/2)	35.10 (0.35-3551.87)	91.0				2 (0/2)	1.93 (0.14-26.84)	97.3
Dried-blood-spot testing	3 (2/1)	2.42 (1.45-4.02)	94.7				1 (0/1)	91.00 (1.46-5656.47)				
Reflex RNA testing				3 (0/3)	9.31 (2.31-37.48)	97.4	1 (0/1)	2.72 (2.17-3.42)				
Opt-out screening	3 (0/3)	18.97 (1.91-188.61)	99.1									
Patient reminders for testing/treatment	9 (4/5)	9.76 (3.99-23.88)	99.9	1 (1/0)	2.16 (0.83-5.63)		2 (2/0)	1.22 (0.75-1.98)	58.5	1 (1/0)	1.32 (0.91-1.92)	
Patient navigation or care coordination				1 (1/0)	1.84 (0.82-4.1)		4 (3/1)	3.25 (2.31-4.57)	0.0	5 (2/3)	2.48 (1.26-4.88)	78.4
Patient education	6 (4/2)	4.18 (1.25-13.96)	95.3				1 (1/0)	0.83 (0.37-1.85)		1 (1/0)	0.82 (0.05-13.39)	
Provider care coordination	2 (1/1)	3.68 (2.12-6.38)	66.9	1 (1/0)	4.56 (1.9-10.9)		2 (0/2)	3.26 (0.57-18.73)	87.3			
Multiple	10 (2/8)	6.73 (4.62-9.81)	99.8	6 (1/5)	2.04 (1.36-3.05)	75.7	7 (1/6)	2.51 (1.55-4.04)	84.4	1 (0/1)	7.79 (4.64-13.08)	
Phased/quality improvement initiative	2 (0/3)	3.14 (2.43-4.05)	82.1	1 (0/1)	75.88 (45.08-127.73)		2 (0/2)	1.02 (0.15-7.1)				
Nurse-led care	1 (0/1)	2.28 (1.47-3.53)								1 (0/1)	15.49 (4.85-49.47)	
Memory practice	2 (2/0)	2.45 (1.5-4.01)	0.0									
Broadened testing/treatment criteria	2 (0/2)	5.84 (0.42-81.13)					1 (0/1)	0.36 (0.11-1.21)		1 (0/1)	1.86 (1.48-2.34)	
Risk-based screening tool	1 (0/1)	3.26 (3.05-3.48)										
Direct solicitation of patients	1 (1/0)	84.69 (68.27-105.07)										
Implementation of systematic testing	1 (0/1)	8.87 (5.55-14.17)										
On-site oral swab collection	1 (1/0)	561.00 (25.69-12252.96)					1 (0/1)	11.45 (1.22-107.51)				
Directly observed therapy	1 (1/0)	1.79 (1.22-2.65)										
Home-based testing	1 (1/0)	0.53 (0.32-0.86)										
Peer support							1 (1/0)	2.55 (0.97-6.7)		1 (1/0)	2.50 (0.92-6.77)	
Motivational interviewing	2 (2/0)	0.86 (0.67-1.1)	0.0							1 (1/0)	3.65 (1.12-11.9)	
Bundled testing	1 (1/0)	1.13 (0.73-1.75)		2 (0/2)	0.99 (0.24-4.16)		1 (0/1)	1.37 (0.7-2.67)				
Financial incentives to patients							3 (1/2)	1.93 (0.75-4.99)	85.1	3 (2/1)	1.37 (0.7-2.67)	47.5
Computer assisted screening tool	2 (2/0)	2.05 (0.73-5.77)	86.6									
Financial incentives to providers	1 (0/1)	130.22 (87.76-193.21)		1 (0/1)	9.25 (0.17-498.62)							
Pharmacist led treatment	1 (1/0)	1.82 (1.46-2.27)								1 (1/0)	1.30 (0.85-2)	
Adherence support	1 (1/0)	1.82 (0.89-3.72)										
Promotional/educational material	2 (2/0)	0.86 (0.62-1.2)										
Modified patient recall	2 (2/0)	0.83 (0.67-1.04)	87.4									
EMR implementation				1 (0/1)	0.76 (0.38-0.67)							
On-site testing				2 (0/2)	19.06 (0.3-1227.45)	94.4				1 (0/1)	0.25 (0.15-0.4)	
Telehealth							2 (0/2)	4.32 (0.48-38.6)	60.9	1 (0/1)	0.32 (0.22-0.47)	

Abbreviations: 95% CI, RCT, randomised controlled trial; NRS, non-randomised study; 95% confidence interval; EMR, electronic medical record;

Figure 1. Prisma flowchart

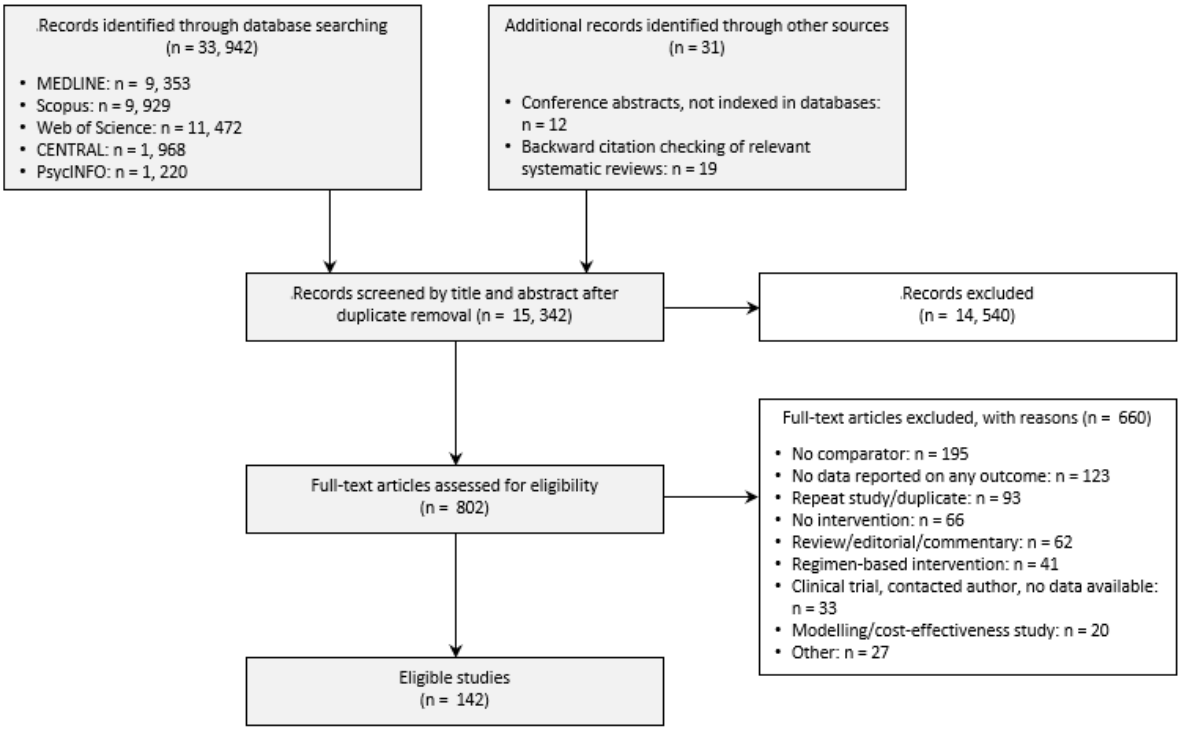


Figure 2. Forest plot examining the association between interventions with two or more studies and HCV antibody testing.

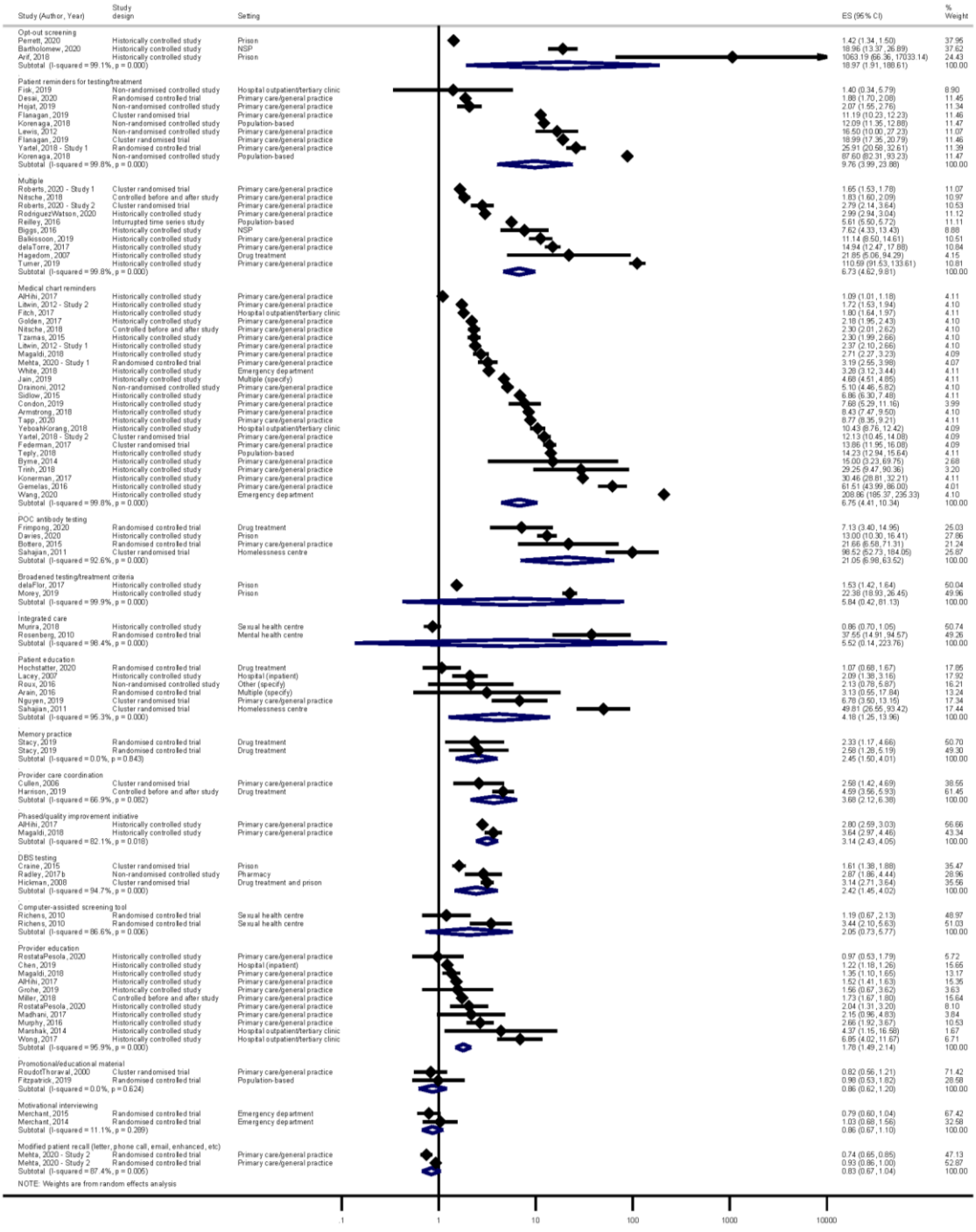


Figure 3. Forest plot examining the association between interventions with two or more studies and HCV RNA testing.

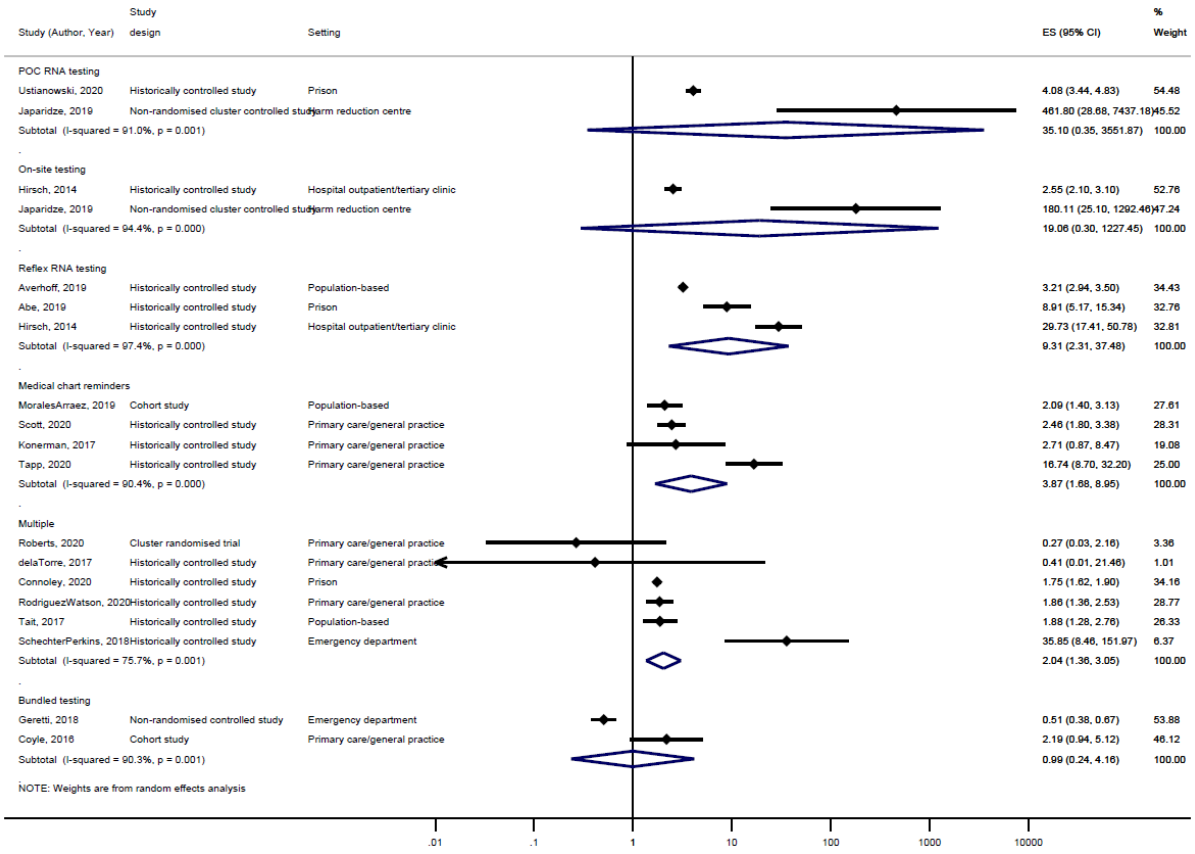


Figure 4. Forest plot examining the association between interventions with two or more studies and linkage to HCV care.

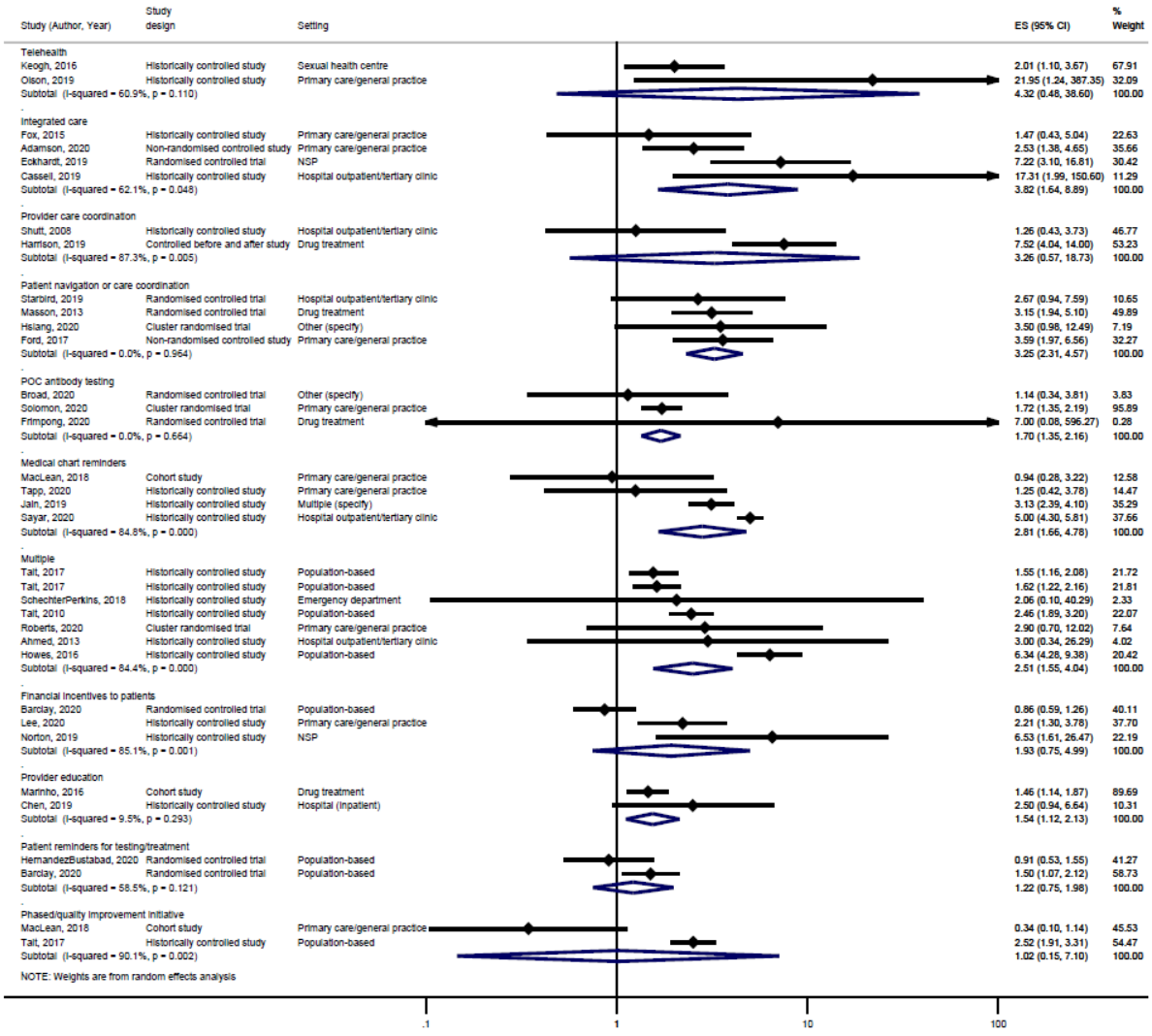
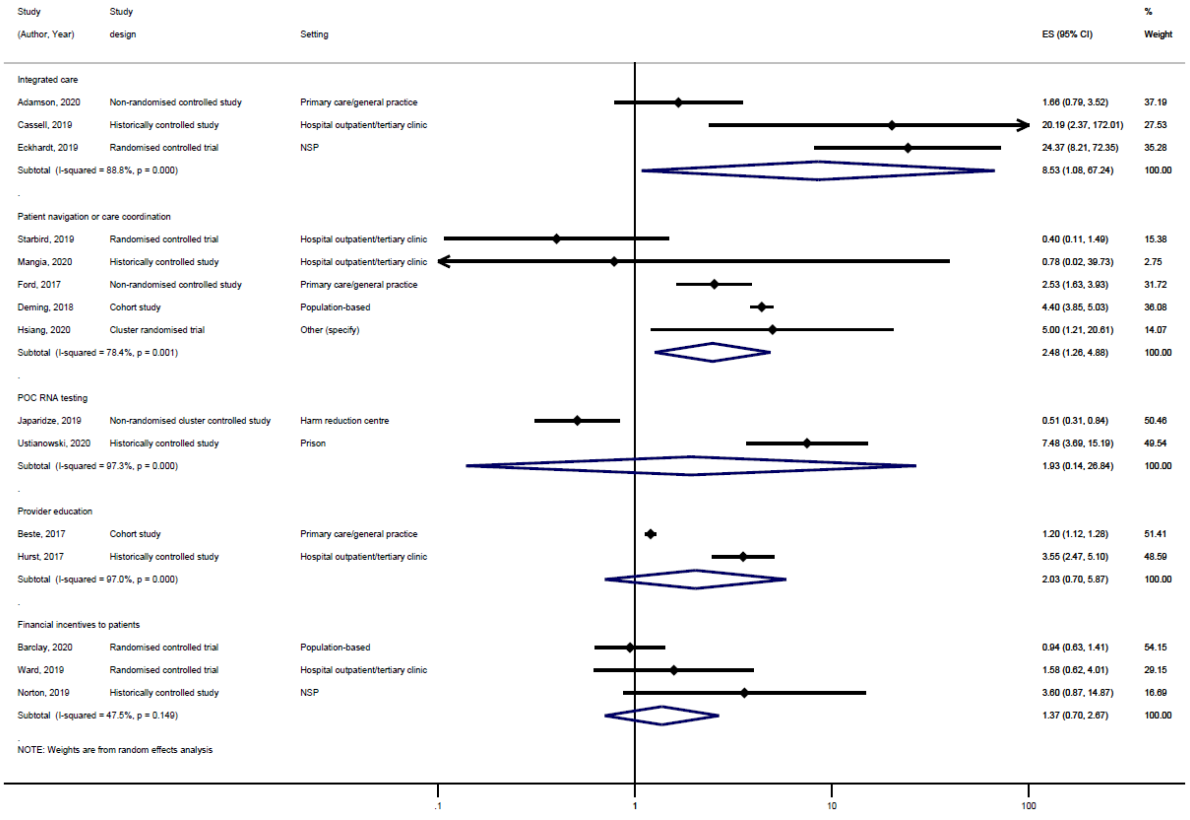


Figure 5. Forest plot examining the association between interventions with two or more studies and DAA treatment initiation.



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