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CADTH HEALTH TECHNOLOGY ASSESSMENT

# Screening for Hepatitis C Virus: A Systematic Review

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## Abbreviations

| | |
|---|---|
| **Ab** | antibody |
| **Ag** | antigen |
| **CDC** | US Centers for Disease Control and Prevention |
| **CERQual** | Confidence in the Evidence from Reviews of Qualitative Research |
| **CLIA** | chemiluminescent immunoassay |
| **CMIA** | chemiluminescent microparticle immunoassay |
| **CTFPHC** | Canadian Task Force on Preventive Health Care |
| **DAA** | direct-acting antiviral agent |
| **ECLIA** | electrochemiluminescent immunoassay |
| **ED** | emergency department |
| **EIA** | enzyme immunoassay |
| **ELISA** | enzyme-linked immunosorbent assay |
| **GRADE** | Grading of Recommendations Assessment, Development and Evaluation |
| **HCV** | hepatitis C virus |
| **ICER** | incremental cost-effectiveness ratio |
| **IDU** | injection drug use |
| **MEIA** | microparticle enzyme immunoassay |
| **PCR** | polymerase chain reaction |
| **PHAC** | Public Health Agency of Canada |
| **PR** | pegylated interferon plus ribavirin |
| **PWID** | people who inject drugs |
| **QALY** | quality-adjusted life-year |
| **RCT** | randomized controlled trial |
| **RNA** | ribonucleic acid |
| **RT-PCR** | reverse transcription polymerase chain reaction |
| **SVR** | sustained viralogical response |
| **USPSTF** | United States Preventive Services Task Force |

# Revision History

| Section | Date | Description/Changes Made | Reason for Change |
|---|---|---|---|
| Objectives | February 2, 2016 | Modified objective to include "viremic": This project will involve a systematic review of published research evidence on the clinical effectiveness, harms, cost-effectiveness, and associated patient preferences and values of screening for hepatitis C virus (HCV) infection in asymptomatic non-pregnant adults; as well as of the diagnostic test accuracy of one screening test available in Canada, the enzyme-linked immunosorbent assay (ELISA) version 3.0 test, compared with the reference standard polymerase chain reaction (PCR) test, for detecting viremic HCV infection in the same population. | To specify the focus on viremic HCV infection, as opposed to situations where antibodies are present, but there is no need for treatment. |
| Research Questions | February 2, 2016 | Modified Question (Q) 5 to include "viremic": What is the diagnostic test accuracy of ELISA version 3.0 test, as compared with the reference standard PCR test, for detecting viremic HCV infection in asymptomatic, non-pregnant, treatment-naive adults with unknown liver enzyme values? | To account for the focused objective, as previously described. |
| Data Synthesis | February 2, 2016 | Modified data synthesis for Q5 to include "viremic":<br>*Diagnostic test accuracy (Q5)*<br>The accuracy of the ELISA version 3.0 test in detecting viremic HCV will be evaluated relative to the qualitative dichotomous PCR test reference standard. | To account for the focused objective, as previously described. |
| Assessment of the Overall Quality of the Evidence Using GRADE | February 2, 2016 | Removed cost-effectiveness (Q3) from the subheading. Added the following statement: There is no tool available to assess the confidence in results of reviews of cost-effectiveness studies. | To explain why no GRADE assessment was conducted for Q3. |
| Inclusion Criteria | March 9, 2016 | Modified population inclusion criteria to include studies that enrolled mixed categories of participants if at least 80% of the study population met the inclusion criteria. Studies that enrolled participants from the general population (including blood donors) without providing details on age, pregnancy status, symptoms, or treatment history were assumed to meet the population inclusion criteria. | To allow for the inclusion of studies with a high degree of relevance to this review that may not have specifically reported on each population inclusion criterion. |

| Section | Date | Description/Changes Made | Reason for Change |
|---|---|---|---|
| Inclusion Criteria | March 9, 2016 | Modified inclusion criteria to allow for the consideration of case-control studies in addition to cross-sectional studies for the diagnostic test accuracy (DTA) question (Q5; protocol previously stated that case-control studies would only be considered if no cross-sectional studies were identified). | To account for inclusion of case-control studies given that few cross-sectional studies were identified. |
| Inclusion Criteria | March 9, 2016 | Expanded setting of interest for the patient preferences question (Q4) to include community and office-based settings, and for the DTA question (Q5) to include laboratory and office-based settings. | To account for the settings that are common and acceptable for these types of studies. |
| Quality Assessment | March 9, 2016 | Modified the quality assessment procedure for Q4 to specify that one reviewer assessed the quality of the study and a second reviewer verified the assessment. | To clarify the method of quality assessment performed for this research question. |
| Research Questions and Inclusion Criteria | August 31, 2016 | Revised the DTA research question (Q5) to a question about clinical validity of all identified screening tests, rather than just the ELISA version 3.0. The PICO table and inclusion criteria were therefore revised to reflect the additional tests, modified outcomes, and focus on studies with a cross-sectional design. | To assess all relevant screening tests, outcomes, and study designs. |
| Risk of Bias | August 31, 2016 | Modified the quality assessment procedure for Q5 to specify that one reviewer assessed the quality of the study and a second reviewer verified the assessment. | To clarify the method of quality assessment performed for this research question. |

# Executive Summary

## The Issue

The Canadian Task Force on Preventive Health Care (CTFPHC) requested a systematic review on screening for hepatitis C to help inform their recommendations. This systematic review will be used along with other resources to develop the CTFPHC recommendations on screening for hepatitis C.[1] The scope of this review was developed with the CTFPHC. This report should not be interpreted as a stand-alone document, and readers are encouraged to consult the CTFPHC's full guideline document.[2]

## Objectives

The objectives are: (1) to assess the published research evidence on the clinical effectiveness, harms, cost-effectiveness, and associated patients' preferences and values of screening for hepatitis C virus (HCV) infection in asymptomatic, non-pregnant, treatment-naive adults; and (2) to assess the published research evidence on the ability of available antibody (Ab) and antigen (Ag) screening tests to identify people in the general population with chronic HCV infection.

## Methods

### Literature Search Strategy

The literature search was performed by an information specialist using a peer-reviewed search strategy according to the PRESS checklist. Published literature was identified by searching the following bibliographic databases MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; the Cochrane Library via Wiley; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. To address the research question related to clinical effectiveness, three separate searches were performed. A broad search for the concept of screening in hepatitis C was performed, and methodological filters were applied to limit the study types to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), and controlled clinical trials. To address the specific concepts of risk- and prevalence-based screening programs, no methodological filters were applied to the search to limit retrieval by study type. To address the research question related to frequency of harms, methodological filters were applied to limit retrieval to safety data. To address the research question related to cost-effectiveness, methodological filters were applied to limit retrieval to economic studies. To address the research question related to people's perspectives and values, methodological filters were applied to limit the study types to health technology assessments, systematic reviews, meta-analyses, RCTs, and non-randomized studies. For all research questions other than clinical validity, retrieval was limited to the human population, English- and French-language documents, with publication dates beginning January 2000. To address the research question on clinical validity, methodological filters were applied to limit the study types to health technology assessments, systematic reviews, meta-analyses, RCTs, and

non-randomized studies. For this research question, retrieval was limited to the human population, English- and French-language documents, and results were not limited by publication date. Conference abstracts were excluded from the search results. Bi-weekly database alerts were established to update the searches until the publication of the final report.

Grey literature (literature that is not commercially published) was identified by searching the Grey Matters checklist. Grey literature search updates were performed in March, April, May, September, and October 2016, as well as February 2017, which included websites of regulatory agencies, health technology assessment agencies, clinical guideline repositories, and professional associations. The searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate content experts and industry.

## Eligibility Criteria

Studies were considered for inclusion if results were reported for asymptomatic, treatment-naive, non-pregnant adults who were at least 18-years-old and had unknown liver enzyme values. For clinical effectiveness, frequency of harms, cost-effectiveness, and patients' preferences, the intervention of interest was any HCV screening method, and the comparator —if appropriate — was no screening. As recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group,[3] prior to the start of the review, outcomes of interest to be assessed in this review for the questions on clinical effectiveness and harms were selected and ranked for clinical importance by members of the CTFPHC's HCV working group and by a sample of 19 adults (including people with and without HCV infection) who represented a cross-section of the general population. For the question on the clinical validity of screening with Ab and Ag tests to identify people with chronic HCV infection, screening tests of interest included Ab tests (e.g., enzyme-linked immunoassay [ELISA], chemiluminescent immunoassays [CLIA], chemiluminescent microparticle immunoassays [CMIA], microparticle enzyme immunoassays [MEIA]), and Ag tests (alone or combination Ab and Ag assays). The diagnostic test for active HCV infection was any polymerase chain reaction (PCR) test that gave a qualitative, dichotomous (positive or negative) outcome. Outcomes of interest were the number or proportion of screening test-positive and screening test-negative patients confirmed to have chronic HCV infection, or confirmed to be virus-free, by PCR.

## Data Extraction

Two reviewers independently extracted data for the research questions on frequency of harms, cost-effectiveness, and clinical validity of screening. Disagreements were resolved through third-party consultation. For the question on patient preferences and values, two reviewers independently inductively coded and captured relevant result statements from each included study. Subsequently, coding structures were compared and discussed until a mutually agreed upon coding structure emerged. No eligible studies were found on the clinical effectiveness of screening.

### Quality Assessment and Risk of Bias Assessment

Following data extraction, for the research questions on clinical effectiveness, harms, and cost-effectiveness, two reviewers independently assessed the quality of each selected study using an appropriate assessment tool specific to the study design. For studies on patients' preferences and values, and clinical validity of screening, one of two reviewers assessed the quality of each study using standardized criteria, depending on the study design. A second reviewer verified the assessments.

### Data Analysis

A narrative synthesis was conducted that involved presenting the results from each included study alongside important study and patient characteristics in narrative and table formats. For the question on the preferences and values related to the decision to be screened for HCV, a thematic analysis was conducted in two stages: coding, and development of descriptive themes.

### Assessment of the Overall Quality of Evidence

The quality of the body of evidence contributing to research questions 1, 2, 3, and 5 was assessed independently by two reviewers using GRADE criteria, including evaluations of study design, risk of bias, indirectness, inconsistency, imprecision, and publication bias. When there was a serious or very serious concern with a criterion, the evidence was downgraded accordingly by one or two levels. Disagreements between reviewers were resolved through discussion or third-party consultation until consensus was reached. The Confidence in the Evidence from Reviews of Qualitative Research (CERQual) approach guided the evaluation of the body of descriptive studies identified for patients' preferences and values (Question 4). Four reviewers used the tool to develop a level of confidence in the review findings, based on an evaluation of the four CERQual components that include the methodological limitations, relevance, adequacy of data, and coherence of the evidence contributing to the findings.

## Results

A total of 12,786 records were identified through the initial database searches. Six-hundred-and- seventy-six (676) of these articles were selected for full-text evaluation. Of these, 40 were selected for inclusion in the review, including one article identified through subsequent alerts. One study each reported on outcomes relevant to frequency of harms, and cost-effectiveness. Twelve studies reported on outcomes relevant to study participants' preferences and values, while 26 studies evaluated the clinical validity of Ab and Ag screening tests. No evidence was found on the clinical effectiveness of screening that matched the study inclusion criteria.

### Clinical effectiveness

No studies that met the selection criteria were identified.

## Frequency of harms

One non-comparative, retrospective database review[4] published in the US in 2008 met the inclusion criteria for the review on frequency of harms. Among 681 anti–HCV-positive patients seen at a Veterans Affairs Medical Center in the US, one out of 520 HCV ribonucleic acid (RNA)-positive patients was hospitalized for pain control following a liver biopsy. Pain was the only reported harm within this study.

## Cost-effectiveness

One cost-effectiveness analysis met the inclusion criteria for this review, and it focused on developing an economic model to project the lifetime health and economic effects of three "screen-and-treat" strategies compared with no screening, in a Canadian context. The screening scenario considered for all strategies was one-time Ab screening offered during a visit to a primary care physician for an unrelated purpose; Ab-positive individuals were followed up with an HCV-RNA test to confirm active infection. Individuals positive on both the Ab and RNA tests were assumed to be referred for treatment, as appropriate, according to Canadian guidelines. For individuals 25 to 64 years of age and living in Canada, screen-and-treat resulted in incremental cost-effectiveness ratios (ICERs) ranging from $34,783 per quality-adjusted life-year (QALY) to $42,398/QALY, when compared with no screening. For individuals 45 to 64 years of age, screen-and-treat resulted in ICERs ranging from $34,359/QALY to $44,034/QALY. One-way sensitivity analyses suggest the model was robust to screening acceptance rates and cost of screening.

## People's preferences and values

Twelve studies provided evidence related to participants' preferences and values regarding the decision to be screened for HCV. The results of these studies revealed that people make decisions about screening while considering their immediate context, and the perceived consequences and implications of a positive test result, including the availability and effectiveness of HCV treatment and concerns about passing on an HCV infection. Furthermore, these decisions are made in various psychological contexts and based on various levels of knowledge about screening and HCV in general. Regarding the implementation of their decision to screen, people generally expressed a desire for confidential and convenient testing in a comfortable environment, and preferred screening situations in which they could appropriately receive sufficient information about HCV and the test, and obtain results quickly. Some issues differed among subsets of the general population, such as concerns about stigma and access to health care among people who inject drugs (PWID) and inmates. Special consideration may be required for these groups.

## Clinical validity of general population screening with Ab and Ag tests

Twenty-six studies were included for the research question on the clinical validity of screening with Ab or Ag tests. Overall, there was a wide range in the proportion of HCV Ab-positive (Ab+) or Ag-positive (Ag+) patients with

active HCV infection (Ab+RNA+ and Ag+RNA+), reported across studies, from 0% to 89.7% with the Ab tests and 0% to 100% with the Ag tests, because of differences in test performance, the underlying HCV prevalence in the source populations, or other sources of population variation between studies. Based on results reported by studies conducted in a general population with a large sample size (n > 1,000), Ab tests appear to be moderately good at identifying individuals with active HCV infection, or HCV viremia, as the proportion of Ab-positive individuals with HCV viremia ranged from 71.0% to 87.5% in these studies.

## Overall Quality of the Evidence

There were no data available to apply GRADE for clinical effectiveness. GRADE was planned but ultimately not used to assess confidence in the findings for frequency of harms, as the evidence came from a single non-comparative study that did not provide an estimate of effect of HCV screening relative to a comparator. GRADE was likewise not used to assess confidence in findings for cost-effectiveness, as the methods for the assessment of evidence derived from cost-effectiveness analysis studies have not yet been established.

A total of five main findings related to participant preferences and values related to HCV screening were evaluated with CERQual. The level of confidence was graded as moderate for the three main findings pertaining to the first descriptive theme: regarding knowledge of HCV and HCV status, implications for management of HCV, and the influence of interpersonal and psychological contexts on the decision to screen. The two main findings related to the second descriptive theme — preferences around implementation and populations with unique barriers to screening — were judged to be findings with low confidence. Overall, assessments of each finding were affected by concerns related to the risk of selection and social desirability biases, insufficient reporting, the relevance of the included study populations and settings, and richness of the data.

The evidence on clinical validity of screening with Ab and Ag tests started out graded as high based on study design. Through an assessment of study design, risk of bias, indirectness, inconsistency, imprecision, and publication bias, the quality of evidence was downgraded. The GRADE of the evidence on each of the clinical validity outcomes was finally assessed as low.

## Conclusions

There is a paucity of clinical trial data regarding the clinical effectiveness and harms of screening compared with no screening; however, that does not necessarily suggest that screening would not be effective in clinical practice. The potential benefits of screening would be closely associated with the underlying prevalence of chronic HCV infection in the screened population and the availability of early treatment for asymptomatic individuals with HCV infection identified by a screening program. With respect to patient preferences and experiences, policy-makers should be aware that individuals make decisions about screening that appear reasonable and feasible within their own life situations, psychological context, and unique knowledge about screening and HCV in general. Individuals also hold

preferences and face barriers regarding the implementation of the decision to screen. Some experiences and views about HCV screening were specific to certain high-risk groups, such as PWID and inmates, which may present important considerations for the implementation of screening programs for these groups. A large range was observed for the proportion of patients who tested positive on both an Ab or Ag test and a PCR test. Based on results reported by studies conducted in a general population with a large sample size (n > 1,000), Ab tests may be acceptable as a first step in a screening pathway. These tests are sufficiently able to identify individuals with active HCV infection, indicated by the presence of viral RNA in blood samples (HCV viremia), as the proportion of Ab-positive individuals with HCV viremia ranged from 71.0% to 87.5% in these studies. The uncertainty introduced by the heterogeneity between study interventions and source populations, as well as the low quality of evidence contributing to each outcome for this review question, precludes clear conclusions about the clinical validity of a particular Ab or Ag test in a screening pathway.

# Introduction

## Hepatitis C Virus

Hepatitis C virus (HCV) is a single-stranded Flaviviridae ribonucleic acid (RNA) virus that may cause acute or chronic infection in humans. Worldwide, it is estimated that 130 to 150 million individuals live with a chronic HCV infection[5] and up to 700,000 deaths occur each year as a result of hepatitis C–related liver diseases.[6] In 2011, an estimated 220,697 Canadians were living with chronic HCV infection, representing a prevalence of 0.64%.[7] Of those living with HCV, it is estimated that as many as 70% are unaware of their condition.[7-11] Prevalence of HCV infection varies among subpopulations based on age and sex.[7,12] Based on HCV prevalence estimates calculated for Canada over a 20-year span, the prevalence of chronic HCV infection is highest in the birth cohort 1955 to 1959 (1.5%), followed by the birth cohorts 1950 to 1954 (1.25%), 1960 to 1964 (1.2%), 1965 to 1969 (1.1%) and 1970 to 1974 (0.8%).[7]

HCV is transmitted primarily through injection or infusion of contaminated blood or blood products. Illicit drug users, inmates, and persons with HIV are associated with a higher-than-average transmission risk,[13] as transmission may occur through the use of contaminated drug paraphernalia, unregulated tattooing and piercing, and blood transfusion with blood that was insufficiently screened for HCV (e.g., blood transfusion performed prior to 1992 in Canada). The risk of transmission during sexual activity is reported to be low, except among HIV-infected men who have sex with men or when there are existing tissue abrasions.[14] Similarly, in pregnant women, the risk of transmission from mother to infant is generally reported to be low, except in the presence of HIV.[15]

Acute HCV infection may be accompanied by fatigue, myalgia, low-grade fever, jaundice, maculopapular rash, and arthralgia, among other conditions.[16] In 15% to 50% of patients, acute HCV infection spontaneously clears without treatment,[9,16] whereas in the remainder of patients, the infection becomes chronic. The progression of HCV infection varies, with some patients experiencing mild liver disease, while in others inflammation and fibrosis may lead to advanced liver damage (cirrhosis), hepatocellular carcinoma (liver cancer), liver failure, or death.[8,17-19] Chronic infection is also associated with a number of extra-hepatic complications including cryoglobulinemic vasculitis, type 2 diabetes mellitus, non-Hodgkin lymphoma, and others, which may contribute to morbidity and mortality.[20]

## Screening, Diagnosis, and Treatment

Screening to identify people with chronic HCV infection typically starts with the use of an enzyme immunoassay (EIA) to detect anti-HCV antibodies (Abs) in the blood. There are a variety of EIAs that can be used for HCV screening, including enzyme-linked immunosorbent assays (ELISAs), chemiluminescent immunoassays (CLIAs), chemiluminescent microparticle immunoassays (CMIAs), and microparticle enzyme immunoassays (MEIAs).

Patients may be considered positive for anti-HCV Abs (Ab+) when their blood samples are reactive with repeat testing on the EIA, or when the presence of Abs has been confirmed by a supplementary Ab test such as an immunoblot or another EIA. However, the presence of Abs (anti-HCV Ab+) indicates exposure to HCV but does not necessarily indicate current or active HCV infection; it may reflect past disease in patients who have spontaneously cleared the infection without treatment or in individuals who have been successfully treated and cured of their infection.[7,9,21] Furthermore, the production of anti-HCV Ab may be delayed by up to 12 weeks following initial infection (known as the "window period"), leading to patients with early acute-stage infection or those who are immunosuppressed being missed by anti-HCV Ab screening conducted during this period before seroconversion.[17] In other words, while the test may accurately provide an Ab– result, it does not necessarily mean that the person is not infected with HCV, only that the individual did not have anti-HCV Ab in the blood at the time of screening.

Active HCV infection is indicated by the presence of viral RNA in the blood, or viremia. As Ab tests detect anti-HCV Abs and do not directly measure viremia, positive HCV EIA test results currently require confirmation of viremia with a nucleic acid amplification test such as the qualitative or quantitative polymerase chain reaction (PCR) test to detect viral RNA.[17] Diagnosis with nucleic acid amplification tests like the PCR test to detect viral RNA is considered definitive; qualitative HCV PCR tests have a reported sensitivity to detect fewer than 50 viral copies per millilitre, and an estimated specificity of over 99.5%.[22] More recent quantitative real-time PCR-based assays have a sensitivity down to approximately 5 IU/mL to 15 IU/mL, with similarly high specificity.[23]

HCV antigen (Ag) can be detected in the blood before the production of anti-HCV Abs;[24] therefore, HCV Ag tests may address the issue of potentially missing cases in the window period. Ag tests may also be introduced as an intermediate test in the screening pathway, with the intent of narrowing the group of Ab+ individuals to receive confirmatory PCR testing to those with evidence of current infection. Unlike Ab tests, Ag tests directly measure a component of the virus and as such indicate active infection; however, Ag tests have been shown to be less sensitive than PCR tests in detecting viral RNA.[23]

The clinical value of a screening test is the ability of a positive test result to properly identify those with active infection, and for a negative test result to correspond to those without active infection. Despite the fact that the presence of anti-HCV Abs does not always indicate active infection in an individual, the value of Ab tests as screening tests for HCV will nevertheless be related to how well those test results correspond with the results of tests (e.g., PCR) that diagnose active HCV infection. Using a PCR test for viral RNA as the sole testing strategy would not be practical because of cost considerations, as well as the risk of false-positive tests due to cross-contamination, which is always a concern in studies using high-volume PCR approaches.[25] The clinical value of a test is distinct from the concept of analytic validity, which is a measure of how well a test detects the signal it was designed to detect — such as the ability of an Ab test to provide a

positive result when Abs are present (analytic sensitivity) and to provide a negative result when Abs are absent (analytic specificity). Third-generation EIAs are commonly used as the initial test in the HCV screening pathway because they have a high sensitivity for the detection of anti-HCV Abs.[22] Analytic sensitivity and specificity are inherent properties of the test, whereas clinical validity will be affected by a number of factors, including the prevalence of HCV in the population; the likelihood that a positive anti-HCV Ab test result will indicate the presence of viremia is higher when there are many people in the population who have active HCV infection, and the likelihood that a negative anti-HCV Ab test result will indicate the absence of viremia is higher when few people in the population are infected with HCV. Appropriate detection of people with chronic HCV infection is critical to identifying those in need of treatment.

Treatment for HCV infection has continued to evolve, with regimens moving away from interferon-alpha- and ribavirin-focused therapy to interferon-free therapy. There are six major genotypes of HCV, labelled 1 through 6, with genotype 1 being the most common in Canada.[16,26] Since 2011, genotype-specific treatment in Canada has included direct-acting antiviral agents (DAA), initially combined with pegylated interferon and ribavirin and more recently in interferon-free oral combinations.[27,28] These DAAs have demonstrated superior efficacy (as measured by sustained viralogical response [SVR]) and are associated with fewer adverse events than pegylated interferon and ribavirin.[29] SVR is a durable end point, with late relapse of infection occurring in less than 1% of individuals.[30] SVR before cirrhosis has developed can be considered a true cure of infection, with no liver-related sequelae and similar survival to an age- and sex-matched uninfected population.[31] SVR in those with cirrhosis is associated with improved quality of life, as well as reduced risk of liver cancer and reduced liver-related and all-cause mortality.[32] SVR does not prevent reinfection in those who are re-exposed to the virus.[33,34] DAA regimens are more expensive per course of therapy than previous treatments.[35] As more people are screened and treated, there is an increased chance of cure but at a higher cost related to the increased cost of treatment.

Advances in treatment options have motivated the development or redevelopment of screening guidelines internationally. In 2012, the US Centers for Disease Control and Prevention (CDC) published guidelines recommending one-time screening for adults born between 1945 and 1965 (i.e., baby boomers).[36] The CDC also recommends ongoing screening for persons with recognized exposure (such as children born to HCV-positive women) or at continued risk for contracting HCV (such as people who inject drugs [PWID]). In June 2013, the U.S. Preventive Services Task Force (USPSTF) updated its 2004 guidelines on HCV screening and now recommends one-time screening for asymptomatic adults either born between 1945 and 1965 or who are at high risk for infection.[37] The USPSTF recommendations were based on a 2012 systematic review on screening for HCV infection in asymptomatic adults without known liver enzyme abnormalities.[38] Most recently, the World Health Organization, or WHO, published guidelines recommending HCV serology testing for individuals from populations with high HCV seroprevalence and for those who have a

history of HCV risk exposure/behaviour.[39] Special attention to subgroups of the population is warranted given that anti-HCV prevalence is associated with age, country of origin, history of injection drug use, homelessness, incarceration, and residence in long-term health care facilities, as reported by the Public Health Agency of Canada (PHAC).[7]

Regarding evidence for screening specific to the Canadian context, the University of Calgary recently released a health technology assessment on HCV screening in Alberta, Canada.[40] The assessment revealed that while key informants generally saw the value of implementing a screening program, there was no consensus on which cohort or cohorts should be prioritized for screening. Access to subsequent treatment was seen as a necessary condition before implementing a screening program. An analysis of the cost-effectiveness of birth cohort (1950 to 1970) screening in Alberta showed that all evaluated combination screening and treatment strategies were cost-effective at a willingness-to-pay threshold of $50,000 per QALY. A budget impact analysis with a time horizon of one year evaluated the costs of screen-and-treat programs for a variety of populations, and determined that they would be the least expensive in pregnant individuals and the most expensive in the general population. Costs would become increasingly expensive as the screening population changed from pregnant individuals to other populations in the following order: inmates, PWID, immigrants, Indigenous populations, the 1950 to 1970 birth cohort, and the general population.

# Objectives

The objectives of this systematic review are (1) to assess the published research evidence on the clinical effectiveness, harms, cost-effectiveness, and associated patients' preferences and values of screening for HCV infection in asymptomatic, non-pregnant, treatment-naive adults, and (2) to assess the ability of available antibody and antigen screening tests to identify people in the general population with chronic HCV infection.

## Research Questions

Question 1: What is the clinical effectiveness of screening for hepatitis C virus (HCV) infection in asymptomatic, non-pregnant, treatment-naive adults with unknown liver enzyme values?

Question 2: What is the frequency of harms associated with screening for HCV infection in asymptomatic, non-pregnant, treatment-naive adults with unknown liver enzyme values?

Question 3: What is the cost-effectiveness of screening for HCV infection in asymptomatic, non-pregnant, treatment-naive adults with unknown liver enzyme values in Canada?

Question 4: What are patients' preferences and values regarding screening for HCV infection in asymptomatic, non-pregnant, treatment-naive adults with unknown liver enzyme values?

Question 5a: What is the clinical validity of anti-HCV antibody testing for general population screening to detect adults with chronic hepatitis C?

- Alone
- In combination with secondary Ab or Ag tests

Question 5b: What is the clinical validity of HCV antigen testing for general population screening to detect adults with chronic hepatitis C?

- Alone
- In dual antibody-antigen tests

# Methods

## Literature search strategy

The literature search was performed by an information specialist using a peer-reviewed search strategy according to the PRESS checklist. The search strategy described here applies to all research questions.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; the Cochrane Library via Wiley; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. To address research question 1, three separate searches were performed. A broad search for the concept of screening for hepatitis C was performed, and methodological filters were applied to limit the study types to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs) and controlled clinical trials. To address the specific concepts of risk and prevalence-based screening programs, no methodological filters were applied to the search to limit retrieval by study type. To address research question 2, methodological filters were applied to limit retrieval to safety data. To address research question 3, methodological filters were applied to limit retrieval to economic studies. To address research question 4, methodological filters were applied to limit the study types to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials and non-randomized studies. For research questions 1, 2, 3, and 4, retrieval was limited to the human population, English- and French-language documents with publication dates beginning January 2000. To address research question 5, methodological filters were applied to limit the study types to health technology assessments, systematic reviews, meta-analyses, RCTs, and non-randomized studies. For research question 5, retrieval was limited to the human population, English- and French-language documents, and results were not limited by publication date. Conference abstracts were excluded from the search results. Bi-weekly database alerts were established to update the searches until February 19, 2017. See Appendix 1 for the detailed search strategy.

Grey literature (literature that is not commercially published) was identified by searching the *Grey Matters* checklist. Grey literature search updates were performed in March, April, May, and September 2016, which includes websites of regulatory agencies, health technology assessment agencies, clinical guideline repositories, and professional associations. The searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate content experts and industry.

## Selection criteria and method

Studies suitable for inclusion were selected from those identified through the literature search using the criteria listed in Table 1 and Table 2.

## Selection method

Four reviewers, in sets of two, independently screened titles and abstracts from the literature search and selected articles that warranted further evaluation. Full texts of potentially relevant articles identified through the initial screen were retrieved and independently assessed by two reviewers for possible inclusion based on the predetermined selection criteria outlined in Table 1 and Table 2. The reviewers made use of the screening checklist found in APPENDIX 2 and compared their lists of included and excluded studies. Disagreements were resolved through discussion or third-party consultation.

## Inclusion criteria

The inclusion criteria were unique to each question. The inclusion criteria for the research questions on the clinical effectiveness of screening (Q1), frequency of screening harms (Q2), cost-effectiveness of screening (Q3), and people's preferences and values related to screening (Q4) are presented in Table 1. The inclusion criteria for the research question on the clinical validity of general population screening with Ab and Ag tests (Q5) are presented in Table 2. With respect to study populations, studies that reported enrolling mixed categories of participants were included if they separately reported results for participants that met the inclusion criteria, or if at least 80% of the study population met the inclusion criteria. Studies that enrolled participants from the general population (including blood donors) without providing details on age, pregnancy status, symptoms, or treatment history were assumed to meet the population inclusion criteria.

As recommended by the GRADE Working Group,[3] prior to the start of the review, outcomes of interest to be assessed in this review for the research questions on clinical effectiveness (Q1) and harms of screening (Q2) were selected and ranked for clinical importance by members of the Canadian Task Force on Preventive Health Care's (CTFPHC's) HCV working group and by a sample of 19 adults (including people with and without HCV infection) who represented a cross-section of the general population; the number of adults with confirmed HCV infection was not reported.[41] The input from the general population sample was gathered by an independent research group with expertise in knowledge translation at St. Michael's Hospital, Toronto, Ontario. All outcomes for Q1 and Q2 were ranked as critical (scores 7 to 9) or important (scores 4 to 6) by at least one of the groups.

For the purposes of this review, the "willingness to be screened" outcome for Q4 is reported as the number or proportion of people who did or would hypothetically accept screening for HCV, when offered. This outcome does not necessarily represent the number or proportion of participants who actually underwent screening in the context of the study or otherwise. It also does not include reporting of the reasoning behind the acceptance or rejection of the offer of screening, as this is captured by the "factors considered in the decision to be screened for HCV" outcome.

## Exclusion criteria

Duplicate publications, companion reports, narrative reviews, case series, case reports, conference abstracts, and editorials were excluded from the responses to all questions. Studies that enrolled mixed categories of participants were excluded if less than 80% of the study population met the inclusion criteria and results were not reported separately for patients who met the inclusion criteria.

For people's preferences related to HCV screening (Q4), studies that reported rates of screening uptake alone, without collecting data from participants directly regarding an offer of HCV screening during the conduct of the study, were excluded from the analysis.

For the question on the clinical validity of general population screening with Ab and Ag tests (Q5), studies were excluded if patient selection was based on known HCV status, increased risk of HCV, or on the basis of a clinical condition that may be associated with chronic HCV infection or that may impact a patient's result on an Ab or Ag test (e.g., patients with hematological malignancies, autoimmune disorders, etc.). Birth-cohort studies that limited inclusion to individuals born from 1945 to 1965 were excluded. While this group represents a subset of the general population, this birth cohort is known to be a high HCV prevalence group for whom screening is recommended in relevant guidelines produced by the CDC[42] and the USPSTF.[37] Studies conducted in "high prevalence countries" (defined as seroprevalence greater than 3.5% based on the CDC classification of HCV prevalence levels[43,44]) according to the seroprevalence value reported for each country by Gower et al.[45] were excluded, as the outcomes for this question (number or proportion of patients who are Ab+RNA+, Ab–RNA+, Ab+RNA–, Ab–RNA–) are affected by population prevalence. Evidence for these outcomes from high HCV prevalence countries is therefore unlikely to be applicable in a Canadian context, where the adult anti-HCV seroprevalence is approximately 1.1%.[45] Studies were also excluded for Q5 if the evaluated interventions were first- or second-generation EIAs. For included studies in which multiple generations of EIAs were assessed, only data pertaining to third- or fourth-generation EIAs were extracted. Studies were excluded if a subset of positive samples or a subset of negative samples from the antibody or antigen testing stage, and not the entire set of samples or patients at enrollment, progressed to the PCR testing stage.

## Table 1: Study Eligibility Criteria for Clinical Effectiveness, Harms, Cost-Effectiveness, and People's Preferences Research Questions

| Clinical Effectiveness (Q1) | Harms (Q2) | Cost-Effectiveness (Q3) | People's Preferences (Q4) |
|---|---|---|---|
| **Population**: Asymptomatic, non-pregnant, treatment-naive adults 18-years-old or older, with unknown liver enzyme values<br>Exclusions: Post-transplant patients, patients with HIV, hemodialysis patients, patients with occupational exposure | | | |
| **Intervention**: Any screening method for HCV infection | | | |
| **Comparator**: No screening[a] | | | |
| **Outcomes**: *Long-term outcomes:* Mortality due to HCV infection, morbidity (including compensated or decompensated cirrhosis) due to HCV infection, HCC, liver transplantation, or quality of life.<br><br>*Intermediate outcomes:* HCV transmission, virologic response, behavioural changes to improve health outcomes, or histological changes. | **Outcomes**: Over-diagnosis, over-treatment, false-positives, false-negatives, harms of follow-up tests (including biopsy), abuse or violence, or anxiety.[b] | **Outcomes**: Cost-effectiveness analysis outcomes (e.g., ICER, ICUR, CBR) or budget impact analysis outcomes. | **Outcomes**: Willingness to be screened and factors considered in decisions to be screened. |
| **Settings**: *Care settings:* Primary care or other settings generalizable to primary care; other settings in which screening is commonly performed (e.g., emergency department, urgent care units)<br><br>*Country setting (cost-effectiveness):* Canada | | | |
| **Study Designs**: RCTs, non-randomized studies with a comparator group, or disease-progression modelling studies[c] | **Study Designs**: RCTs, non-randomized studies with or without a comparator group, or disease-progression modelling studies | **Study Designs**: RCTs, economic evaluations, and economic modelling studies | **Study Designs**: Descriptive studies (surveys, qualitative) and mixed-methods studies |
| **Languages:** English and French | | | |
| **Search Time Frame:** January 2000 to March 2016 | | | |

CBR = cost-benefit ratio; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; RCTs = randomized controlled trials.
[a] Descriptive studies, mixed-methods studies, and observational studies without a comparator group were exempt from this requirement.
[b] Data relevant to change in insurance premiums, labelling, or partner discord, if located within the planned search, were included in this review. It is possible that research into the impact of HCV screening on these outcomes is published in databases not included in the search strategy.
[c] Disease-progression modelling studies for Q1 and Q2 were defined as studies with a stand-alone disease-progression model, developed independently of an economic model or cost-effectiveness analysis. Economic modelling studies were included for Q3.

## Table 2: Study Eligibility Criteria for Clinical Validity of General Population Screening With Ab and Ag tests (Q5)

| Inclusion Criteria (Q5) | |
|---|---|
| **Population** | General population adults (asymptomatic, non-pregnant individuals 18-years-old or older, with unknown HCV status and unknown or normal liver enzyme values)[a]<br>*Exclusions:*<br>Individuals from high-risk groups (e.g., HIV-positive patients, PWID, patients with occupational exposure, inmates, post-transplant patients, hemodialysis patients, patients who received a blood transfusion prior to 1992,[b] and clients of sex workers);<br>Individuals from high-prevalence groups (e.g., 1945 to 1965 birth cohort, individuals living in or who have emigrated from a high-prevalence country[c]) |
| **Screening Test** | **Q5a:** Anti-HCV Ab assays (e.g., ELISA, CMIA, CLIA, EIA, MEIA) alone or in combination with secondary Ab or Ag testing, with or without supplemental or confirmatory tests (e.g., immunoblot[d])<br>**Q5b:** HCV Ag assays or combination HCV Ag-Ab assays, with or without supplemental or confirmatory tests (e.g., immunoblot[d])<br>*Exclusions:*<br>Anti-HCV rapid tests |
| **Diagnostic Test** | Dichotomous (positive-negative) PCR test to detect HCV-RNA |
| **Outcomes** | **Q5a:**<br>Proportion or number of patients who are Ab-positive and RNA-positive (Ab+RNA+);<br>Proportion or number of patients who are Ab-negative and RNA-negative (Ab–RNA–);<br>Proportion or number of patients who are Ab-positive and RNA-negative (Ab+RNA–);<br>Proportion or number of patients who are Ab-negative and RNA-positive (Ab–RNA+)<br>**Q5b:**<br>Proportion or number of patients who are Ag-positive and RNA-positive (Ag+RNA+);<br>Proportion or number of patients who are Ag-negative and RNA-negative (Ag–RNA–);<br>Proportion or number of patients who are Ag-positive and RNA-negative (Ag+RNA–);<br>Proportion or number of patients who are Ag-negative and RNA-positive (Ag–RNA+) |
| **Settings** | *Care settings:* Primary care or other settings generalizable to primary care; other settings in which screening is commonly performed (for example, emergency department, urgent care units), as well as laboratory and office-based settings<br><br>*Country settings:* Low-to-moderate HCV prevalence countries[c] |
| **Study Designs** | Cross-sectional |
| **Languages** | English and French |
| **Search Time Frame** | Until June 2016 |

Ab = antibody; Ag = antigen; CLIA = chemiluminescent immunoassay; CMIA = chemiluminescent microparticle immunoassay; EIA = enzyme immunoassay; ELISA = enzyme-linked immunosorbent assay; HCV = hepatitis C virus; MEIA = microparticle enzyme immunoassay; PCR = polymerase chain reaction; PWID = people who inject drugs; RNA = ribonucleic acid.

[a] Blood donors were assumed to be representative of the general population.

[b] Or prior to whatever year was specified in the publication as the start date of blood screening for HCV in that particular region.

[c] " High-prevalence" was defined as HCV seroprevalence of higher than 3.5%, "low-to-moderate HCV prevalence" was defined as HCV seroprevalence of 3.5% or lower.[44] Countries with an HCV seroprevalence point estimate higher than 3.5%, as reported by Gower et al.,[45] were classified as high-prevalence countries; studies of people living in or emigrating from these countries were excluded.

[d] Excluding recombinant immunoblot assay, or RIBA.

## Data extraction

Data were extracted from each study on the inclusion list that were relevant to the outcomes predefined in the protocol, and entered into standardized tables as found in Appendix 3. Data from figures were not used if the data points were not explicitly labelled. For all studies, descriptive data were also extracted, including information on authors, design of the study, year of publication, country, care setting, participant characteristics, description of the intervention, description of comparators (if appropriate), conflicts of interest, and financial sponsorship. Aditionally, for Q3, descriptive data included perspective of the analysis, sources of utilities, main assumptions, and planned sensitivity analyses. The reviewers did not have reason to contact authors to request missing information, clarify issues, or verify extracted data.

No eligible studies were identified for Q1, and therefore no relevant outcome data were extracted. For Q2 and Q3, two reviewers independently extracted descriptive and outcome data from each included study.

For Q4, two reviewers independently inductively coded and captured statements from the results section from each included article that were relevant to the research question for subsequent analysis using NVivo qualitative data analysis software (QSR International Pty Ltd., Version 11, 2015).[46] For further details, refer to the Data analysis methods section that follows. Prior to coding, each result statement was assessed to ensure it was differentiated from raw data, methods, external data, and researchers' conclusions and implications; result statements meeting these criteria were coded.[47] Variables statistically associated with the uptake of screening (e.g., age, sex) were not extracted from included studies because these data are not directly related to participant willingness to be screened, and are therefore outside the scope of this review.

For Q5, one reviewer extracted descriptive and outcome data and the other verified the accuracy of data extraction.

The reviewers met frequently throughout the process to discuss discrepancies. Disagreements were resolved through discussion or third-party consultation.

## Quality or Risk of Bias assessment

Following data extraction, an assessment of the quality of each selected study was made using an appropriate assessment tool specific to the study design. For Q2 and Q3, two reviewers independently assessed study quality. For Q4 and Q5, one reviewer assessed the quality of each study and a second reviewer verified the assessments. A Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions[48] guided comments on the quality of the study that was deemed eligible to answer Q2, and the Drummond checklist[49] was applied to the cost-effectiveness study (Q3). For Q4, qualitative studies were assessed using criteria outlined in the Critical Appraisal Skills Programme checklist,[50] and survey studies were assessed using standardized criteria including clarity and

appropriateness of study methods, with particular attention paid to sampling decisions, validity, and reliability of data collection methods, and the comprehensiveness of reporting.[51,52].The QUADAS-2 tool[53] was applied to critically appraise the studies on the clinical validity of general population screening with Ab and Ag tests (Q5).

During deliberations, the reviewers documented information used to support the quality judgments. Reviewers resolved disagreements in appraisals through discussion or third-party consultation if consensus could not be reached.

## Data analysis methods

### Frequency of harms, cost-effectiveness, and clinical validity of screening with Ab and Ag tests

While a meta-analysis of outcome data was planned, it was not appropriate given one study each met the criteria for the questions on frequency of harms and cost-effectiveness. No studies were identified for the question on clinical effectiveness. For the question on the clinical validity of screening tests, meta-analysis was likewise planned but not conducted given the observed clinical heterogeneity across included studies. For each research question, a narrative synthesis was conducted that involved presenting the results from each included study alongside important study and patient characteristics believed to contribute to the observed heterogeneity in narrative and table formats.

### Patient preferences and values

For the question on the preferences and values related to the decision to be screened for HCV, a thematic analysis was conducted. The analysis was conducted in two stages: coding and development of descriptive themes. The analysis was conducted using NVivo qualitative data analysis software (QSR International Pty Ltd. Version 11, 2015).[46]

In the first coding stage, two reviewers independently reviewed the results reported within the full-text articles, and assigned codes to concepts, ideas, and categories relevant to the research question. Initial codes were applied in the context of the outcomes (from the PICO) including people's willingness to be screened; factors considered in decisions to be screened; barriers and facilitators to screening; and preferences, values, and attitudes about screening. More codes were developed iteratively, as new concepts emerged as the analysis progressed.

To begin coding, the first three study reports were coded independently by the two reviewers. A team meeting was then held during which coding was compared and discussed, with discrepancies resolved and corresponding refinements made to the coding template. The next three reports were then coded independently, with another team meeting to allow for comparison, discussion, and refinements to the coding template. Given the high level of agreement between the researchers in terms of coding at this point, the remainder of the articles were coded by one reviewer and verified by the

second reviewer. Regular discussions among the research team enabled organization, code refinement, and reflection upon a wide range of interpretations across the body of research identified. When all codes were applied to the full sample of results, all of the text assigned to each code was read independently by two reviewers to assess consistency in interpretation and application, and to determine whether any additional levels of coding were required. Refinements were made, as required, to the coded text and definitions were developed for each code to reflect the data captured within.

In the second stage of the analysis, the codes developed in the prior stage were organized into related areas to construct "descriptive themes." In this process, four reviewers met to assess similarities and differences between the codes, and grouped together all similar codes into unique themes. At this stage, reviewers determined whether emergent themes were transferable across different studies, and whether some apply to some populations but not others. Once descriptive themes were identified, a draft summary of the results across the studies organized by each theme was written by one reviewer and subsequently reviewed by a second reviewer. The final version was agreed upon by three descriptive review team members and reviewed by a fourth. It represents a synthesis that closely reflects the original results of the included studies, with minimal interpretation.

## Assessment of the Overall Quality of the Evidence Using GRADE and CERQual

No study met the inclusion criteria for Q1; therefore, a GRADE assessment could not be made.[54] A GRADE assessment was planned to assess confidence in the findings for Q2 but ultimately not conducted. According to the GRADE handbook, "the [GRADE] system is designed for reviews and guidelines that examine alternative management strategies or interventions, which may include no intervention or current best management as well as multiple comparisons."[55] The evidence on frequency of harms (Q2) came from a single non-comparative study of the harms observed in a group of patients who went through one-time screening for HCV. As the study did not provide an estimate of effect of HCV screening relative to a comparator, the reviewers did not apply GRADE. GRADE was likewise not used to assess confidence in findings for Q3, as the methods for the assessment of evidence derived from cost-effectiveness analysis studies have not yet been established. According to the section 6.3.4.6 Economic Model of the GRADE handbook, the GRADE working group does not recommend incorporating cost-effectiveness models into evidence profiles given that economic models include a number of assumptions and evidence from multiple sources of varying quality.[55]

The Confidence in the Evidence from Reviews of Qualitative Research (CERQual) approach[56] (contained in the GRADE methodology tool box) guided the evaluation of the body of descriptive studies identified for Q4 of this review. The tool was used to develop a level of confidence in the review findings, based on an evaluation of the four CERQual components that include the methodological limitations, relevance, adequacy of data, and

coherence of the evidence contributing to the findings. Findings were assessed independently by one of two reviewers. Review authors were aware of the interactions between the four components of CERQual and gave equal weight to each component, while recognizing overlap between them. The reviewers began with an assessment of methodological limitations and then assessed the other three components in an iterative fashion. Each review finding began with a high level of confidence, which was reduced according to the severity of concerns about the evidence in any of the four CERQual domains.

Four reviewers met to discuss the initial CERQual assessment of the findings and come to consensus on the level of confidence. The reviewers discussed the judgments and developed a clear description of the rationale behind each assessment. Participation by multiple reviewers from different disciplinary backgrounds, including reviewers with experience in primary qualitative research and qualitative evidence synthesis, helped shape the interpretations of confidence.[56]

Two reviewers used GRADE criteria to evaluate the evidence for Q5.[57] These criteria were based on study design, risk of bias, indirectness, inconsistency, imprecision, and publication bias. When there was a serious or very serious concern with a criterion, the evidence was downgraded accordingly by one or two levels. Disagreements between reviewers were resolved through discussion or third-party consultation until consensus was reached.

# Summary of Evidence and Data Synthesis

## Quantity of research available

A total of 12,786 records were identified through the initial database searches. Six-hundred-and-seventy-six (676) of these articles were selected for full-text evaluation. Of these, 40 were selected for inclusion in the review, including one article identified through subsequent alerts.[58] One study each reported on outcomes relevant to frequency of harms,[4] and cost-effectiveness.[35] Twelve studies[58-69] reported on outcomes relevant to study participants' preferences and values, while 26 studies[24,70-94] evaluated the clinical validity of general population screening with Ab and Ag tests. Appendix 4 presents the PRISMA flow charts.[95] Lists of excluded studies, with reasons for exclusion, are provided in Appendix 5.

For each research question, narrative summaries of study characteristics, patient characteristics, quality assessment, and data analysis are presented in text format. Details can be found in table format in Appendix 6, Appendix 7, Appendix 8, and Appendix 9 respectively.

## Research question 1 — Clinical effectiveness

No studies reporting on the clinical effectiveness or benefits of screening were identified.

## Research question 2 — Frequency of harms

### Study characteristics

One non-comparative, retrospective database review[4] conducted in the US in 2008 met the inclusion criteria for the question on frequency of harms.

Based on a retrospective review of a database of outpatient visits at a large urban Veterans Affairs Medical Center in Minneapolis, the authors examined results from 12,485 HCV EIA antibody tests. Patients who had tested positive for HCV Ab and HCV-RNA between January 2000 and December 2001 were first identified. From this set, 681 patients who had multiple positive tests within an expanded time frame from January 1992 to December 2001 were identified. The records of the selected patients were evaluated to determine referral rates to hepatitis clinics, reasons for non-referrals, and the proportion of patients who successfully attended one or more referral appointments for HCV specialty care. Eligible patients were referred for treatment. Clinical outcomes, including adverse effects associated with screening and treatment, were evaluated. Statistical analysis was performed for the association of patient characteristics, with referral and presentations at appointments.

The study authors disclosed their funding from government support. The study authors also reported an author receiving a grant from industry support. The authors declared no conflicts of interest.

Additional details can be found in Table 7 in Appendix 6.

### Patient characteristics

The average age of participants was 53.5 ± 8.4 years. Females made up 3.1% of this population. Of the total, 50.3% were white, 34.4% were of unknown ethnicity, and 15.3% were minorities (predominantly African-American). Sixty-nine per cent of the population was unmarried. The percentage who had prior psychiatric diagnosis, a major medical comorbidity, psychiatry prescriptions, or narcotic prescriptions were 34.4%, 22.1%, 28.0%, and 22.5%, respectively.

Additional details can be found in Table 11 in Appendix 7.

### Risk of bias assessment

The study strengths were mainly associated with clear reporting; study objectives and main outcomes were clearly described, and patient inclusion criteria were provided. Patients who tested positive for anti-HCV Ab were tested with PCR. Selection bias was suspected, as samples were enrolled retrospectively based on PCR test results; however, it is unclear how this would affect the outcome of harms due to HCV screening. The main findings of the study were clearly reported. Other than missing diagnostic test results from fewer than 2% (11 out of 681) of samples, bias due to deviations from the intended interventions was not evident. Bias in the application of the intervention could not be assessed, as samples were enrolled retrospectively. Potential bias due to measurement of outcomes could not be assessed, as the process with which harms were measured was not adequately described. Specific harms outcomes of interest for the study were not described in the methods, so it is unclear whether selective outcome reporting occurred.

### Data analysis and synthesis

A total of 670 (out of 681) patients received confirmatory PCR tests for HCV-RNA and 520 were positive. From the population of screened patients, one patient was hospitalized for one night for pain control following a liver biopsy. No fatalities were reported in the cohort of patients who had liver biopsies or treatment, and no information was reported on over-diagnosis, over-treatment, false-positives, false-negatives, abuse or violence, or anxiety. Information on change in insurance premiums, labelling, or partner discord was also unavailable.

Additional details can be found in Table 9 in Appendix 8.

## Research question 3 — Cost-effectiveness

### Study and patient characteristics

One study[35] met the inclusion criteria for the question on cost-effectiveness. The objective of the study was to develop an economic model to project the lifetime health and economic effects of various "screen-and-treat" strategies for HCV in Canada. The primary motivation was to determine the applicability of one-time, age-specific cohort screening programs and subsequent treatment regimens. The study was published in 2015 and incorporated estimates from Canadian and international data sources.

The authors of this study conducted a cost-utility analysis based on a cohort state-transition model. Using the 2011 Canadian population census, individuals between the ages of 25 and 64 (i.e., corresponding to the birth years of 1946 through 1985) were included in the model. One-time screening programs to identify patients with chronic HCV monoinfection followed by treatment options were compared with a "no screening" option. Screening consisted of a blood test for HCV Ab, and in patients with a positive Ab test, this would be followed by a test for HCV-RNA to confirm the infection. The study assumed that all HCV-RNA-positive individuals would be referred to a hepatologist, gastroenterologist, or infectious disease specialist and would be offered treatment according to the Canadian guidelines available at the time. The treatment scenarios were: pegylated interferon plus ribavirin (PR) for all patients (described here as "Tx1"); simeprevir plus PR for patients with genotype 1; sofosbuvir plus ribavirin for patients with genotypes 2 and 3; PR for patients with genotypes 4, 5, and 6 ("Tx2"); interferon-free combination therapy for patients with genotype 1; sofosbuvir plus ribavirin for patients with genotypes 2 and 3; and PR for patients with genotypes 4, 5, and 6 ("Tx3").

The state-transition model had patients moving through various health states at weekly cycles until death. Health states captured included the progression of hepatitis C infection without fibrosis, fibrosis stages F0 to F4, advanced liver disease, and treatment and treatment-related adverse events. Disease-progression parameters, probabilities of transition to advanced liver disease, mortality rates, treatment-related efficacy, epidemiologic variables, and direct costs were extracted from the literature. Utilities for each health state were taken from a Canadian utility study published in 2012 based on the Health Utilities Index Mark 2. Outcomes were expressed in terms of costs per quality-adjusted life-year (QALY), with the costs captured reflecting the payer's perspective. Future costs and health benefits were discounted at 5%.

The authors disclosed that their funding came from government support. The study also declared competing interests, as one of their authors received grants and/or consulting fees from various industry supports.

Additional details can be found in Table 8 in Appendix 6.

## Quality assessment

Wong et al.[35] evaluated the impact of screening and treatment on a birth cohort from the Canadian population. The model parameters related to HCV seroprevalence, genotype distribution, and awareness of personal HCV infection were appropriate and derived from literature pertaining to a Canadian population. The acceptance rate when screening was offered was assumed to be 91%, which seems to be appropriate given the high acceptance of screening identified in this review (Table 19). Other assumptions specific to the population included the rate at which undiagnosed patients would discover their HCV infection over their lifetime, and an independence in the distribution between fibrosis stage and genotype distribution (i.e., among patients with HCV infection between the ages of 25 to 34, 20% of patients are at fibrosis stage F0 and 36% of patients are at fibrosis stage F1, regardless of the HCV genotype). The latter assumption is not expected to greatly impact the screening component of the model, as HCV genotype and fibrosis stage do not influence screening rates. However, the probability of treatment is dependent on both of these factors.

The screening portion of the intervention in this model was a one-time screening strategy involving an initial blood test for HCV Ab followed by a test for HCV-RNA if Ab results were positive. Repeat screening — for patients with known risk factors, for example — was not considered. The screening strategy was not universal, as it focused on a specific birth cohort. This strategy is generally relevant to this review, although it did not address other populations or subgroups of interest, such as unselected members of the general population (outside of the birth cohort studied) or high-risk individuals.

As with all models, some assumptions may be questioned. For example, the model assumed that all individuals who tested positive for HCV Ab would proceed to an HCV-RNA diagnostic test, and it was unclear whether a reflex testing strategy (sufficient blood sample for screening and diagnostic testing taken at the first visit) or a recall testing strategy (screening test-positive patients recalled for a second sample for diagnostic testing) would be used. Furthermore, it was assumed that all test-positive individuals would be referred to a specialist to pursue one of the three modelled treatment options. In reality, fewer than 100% of individuals may return for the diagnostic test in a recall testing strategy or attend subsequent appointments with specialists if diagnosed with HCV infection, which may mean that the model overestimated both the costs and clinical effectiveness outcomes of screening. While these factors were not explicitly addressed, patient loss to follow-up for any reason was indirectly evaluated in sensitivity analyses that modified the probability of receiving treatment. Sensitivity analyses showed that changes in the probability of receiving treatment did not alter the overall conclusions. Although the scope of the economic study was on “screen-and-treat” strategies, the screening component of the model was poorly described when compared with the treatment component. It is difficult to assess the validity of the parameters used in the screening

component of the model, as sensitivity and specificity for each test were not reported.

Appraisal of the overall economic evaluation, based on the Drummond Checklist, can be found in Table 14 in Appendix 8.

### Data analysis and synthesis

In the base case, for individuals 25 to 64 years old, the incremental cost-effectiveness ratio (ICER) of screening and Tx3 over "no screening" was $34,783/QALY. When compared with no screening, the other options had ICERs of $38,117/QALY (Tx1) and $42,398/QALY (Tx2). When compared with screening and Tx3, Tx1 and Tx2 were either dominated (i.e., more costly, less effective) or extendedly dominated (i.e., less costly and more effective to give a proportion of patients no screening, and the remaining proportion screening and Tx3). For individuals 45- to 64-years-old, screening and Tx1 would be considered the most cost-effective strategy at an ICER of $34,359/QALY, followed by Tx3 ($35,562) and Tx2 ($44,034). One-way sensitivity analysis suggests that the model was robust to screening acceptance rates and cost of screening. When compared with no screening only, probabilistic sensitivity analyses demonstrated that the chance that screening and treatment would cost less than $50,000/QALY was 56% for Tx1, 51% for Tx2, and 60% for Tx3.

Details can be found in Table 18 in Appendix 9.

## Research question 4 — People's preferences and values regarding HCV screening

### Study characteristics

A total of 12 studies[58-69] were identified that evaluated participants' preferences and values regarding the decision to be screened for HCV infection. Nine studies exclusively used a descriptive survey design and collected data via a researcher-administered or self-administered questionnaire,[58-60,62-64,66,68,69] two had a qualitative descriptive design that employed a semi-structured interview method,[65,67] and one used a mixed-methods approach of sequential quantitative survey (questionnaire) and qualitative description (semi-structured interview).[61] The included studies were conducted in the US,[58,60-64,69] UK,[67,68] Canada,[59] the Netherlands,[65] and Australia,[66] and were published between 2006 and 2015. All but one study[63] had ethics approval. The studies were conducted in a variety of primary care and non-primary care settings, including hospitals, community health and resource facilities, specialized health care clinics, correctional facilities, and university research centres. The sample sizes of the included studies ranged from 30[67] to 1,012[59] participants. Participants were surveyed or interviewed about their views and preferences regarding HCV screening, based on their experiences with testing in the current study,[58,60,62,65,66] previous experience with testing,[61,96] or their hypothetical acceptance of proposed future HCV testing.[68,69] Three studies did not report the setting of HCV testing.[59,63,64]

All studies disclosed their sources of funding, which included research grants and fellowships,[59,61,63-66,69] government funding,[62,63,66-68] and industry support (grants or products).[58-60] Three of the studies[58,60,66] did not report on conflict of interest, but nine of the studies[59,61-65,67-69] reported no conflicts of interest.

Additional details on study characteristics can be found in Table 9 in Appendix 6.

## Participant characteristics

A variety of population types were targeted by the identified studies, including a general population of patients who were attending health care clinics unrelated to HCV,[64,68] a high HCV prevalence birth cohort (the "baby boomer" generation born from 1945 to 1965),[58-60] and people who are at high risk for contracting HCV due to injection drug use (IDU),[60-63,66] incarceration,[67,69] or any one of several known risk factors, including a history of blood transfusions and having the skin pierced in a high HCV prevalence country.[65] The majority of participants in one study[58] were immigrants to the US (race not specified).

Details on participant characteristics can be found in Table 12 in Appendix 7.

## Quality assessment

In general, the 10 studies that collected data through a survey allowed for the collection and analysis of data related to the perspectives, preferences, and experiences of HCV screening that influence the decision to be screened from the perspective of a variety of subgroups within the general population. In all studies, participation rates ranged from 30% to 96%, and sample sizes ranged from 30 to 1,012 participants. In some cases, substantial effort was expended to recruit individuals from marginalized and vulnerable populations who are likely to benefit from screening programs but who do not regularly access health care services. However, one study[63] that included homeless individuals and PWID was exempted from ethics review; this introduces uncertainty about the appropriateness of the study recruitment and conduct, which included the provision of a small financial incentive for participation. Among the survey studies, none included descriptions of the validity or reliability of questions asked. While in some cases, questionnaires used in other studies were modified and reused in the included studies, the validity and reliability of those questionnaires was likewise not discussed. In some instances, validity was a concern; for example in one study designed to assess the acceptability of HCV screening in a general population,[64] questions regarding preferences and reasons for and against testing were not asked. Further, in several cases social desirability bias was a concern when, for example, a nurse or other health care worker administered a questionnaire. Given the sensitive nature of the topic (e.g., HCV screening, risk factors), it is likely that participants responded in a way they felt would satisfy the interviewer, as the health care worker was involved or could potentially be involved in the care of the participant. In most cases, the survey studies were limited in that they did not enable participants to express their views in their own words but instead required participants to identify their views from a predetermined,

researcher-developed list. Generalizability is another concern across most survey studies. In particular, the views of people who do not regularly access health services, or who do not want to be screened, were not included in some studies. Finally, in several studies, there was neither discussion regarding the potential implications for selection bias nor any related ethical concerns, such as the provision of a financial incentive for completing questionnaires.

Three studies[61,65,67] involved the collection of in-depth qualitative data to respond to research questions related to the experience of HCV screening and factors related to the decision to pursue screening. A major strength of these studies is that the issues that are important to participants could emerge through participant's descriptions using their own words, as opposed to responding to items in a researcher-developed list. One such study also collected quantitative data, which provided an opportunity to explore issues of importance to PWID, as well as the frequency of such issues in a large sample (n = 520).[61] In this study, however, this opportunity was not fully explored, as results from both components of the study were not integrated. None of the qualitative studies included a discussion of the position or background of the researcher and their relation to the study subject. This lack of information raises concern regarding the trustworthiness of the data, as it is unclear how the researchers' preconceptions and prior understanding of the issue influenced study design, data collection, and analysis. One of the three qualitative studies[65] mentioned sampling until saturation, and described an iterative process of data collection and analysis as is typical in qualitative research; the other two[61,67] did not provide any justification for the sample size.

Details of the strengths and limitations for each study can be found in Table 15 in Appendix 8.

## Data analysis and synthesis

When participants in the included studies discussed their willingness and preferences around screening, they extended their considerations to include issues related to the implementation of their decision to be screened, or not to be screened, and relied heavily on their perceptions of the implications of learning their HCV status. It further became apparent that the decision to screen and perceptions about screening occur within specific contexts of varying populations, including personal knowledge about HCV, psychological health, lifestyle choices, and relationships with others.

Two main descriptive themes emerged surrounding people's perspectives of screening and willingness to be screened:

1. People decide whether to be screened for HCV while considering the perceived implications of their decision and learning their results.
2. People have preferences around and face barriers regarding the implementation of their decision to screen.

The first descriptive theme summarizes the elements of a decision-making process regarding HCV screening that were reported by participants in the included studies. People considered whether they wanted, needed, or should pursue screening based on their current situation but also while considering downstream events related to a decision to undergo screening and of receiving the test result. The second descriptive theme includes the preferences, values, and experiences around the implementation of screening given, or in spite of, the participant's decision to undergo screening. The concepts explored within this theme include barriers and facilitators to HCV screening, and preferences around the conduct of screening.

Additional information can be found in Appendix 9. Regarding participants' willingness to be screened, quantitative data that were reported alone (i.e., without an associated evaluation or discussion of participants' views and preferences around willingness to be screened) are provided in Table 19.

## Descriptive Theme 1

People decide whether to be screened for HCV while considering the perceived implications of their decision and learning their results.

### *Knowledge of and desire to know HCV status, level of perceived personal risk, and knowledge of HCV influence the decision to be screened.*

Participants' lack of knowledge about their HCV status, and the desire to know their status, emerged as reasons both for and against HCV screening. One study that assessed support for universal HCV screening in hospital reported that 87% of surveyed medical centre outpatients would want to know if they had HCV, and that these patients were significantly more likely to be in favour of universal screening for HCV than those who did not want to know if they had HCV.[64] When participants described their reasoning on this topic, some people indicated that they wanted to know their HCV status because they were uncomfortable with uncertainty: "Not knowing sucks. It doesn't feel good when you don't know if you have it or not."[61] Other patients focused on seeking "peace of mind" or a sense of reassurance provided by the confirmation of a negative test.[65,68] For example, "I wasn't afraid that something was wrong but, yes, I wanted to be sure."[65] Other participants reported wanting to know their HCV status irrespective of any other reasons. For example: "Well, I tested because I think, 'Well, I want to know, finish this, just do it.'"[65]

Alternatively, some participants would decline HCV screening because they knew or thought they had already been tested for HCV, or they already knew their HCV status.[58,65,68,69] Others would decline screening because they did not want to know at all if they had HCV,[69] yet some reported they would not want to be tested at a particular time, citing that they were "not ready"[61] or that they "would want to think further about the implications of the results before [they were] tested."[68] Some participants simply did not think that knowing either way would matter; in a study of PWID surveyed about their reasons for delaying testing, 27% agreed with the statement "knowing my status wouldn't change anything."[66]

When participants did not know their status, their perceived risk of HCV also influenced their decision regarding HCV screening; certain people were willing to pursue screening because of a high perceived personal risk of HCV, while others felt screening to be unnecessary because of a low level of perceived personal risk.[61,65,66,68] However, acceptance of HCV screening was not always dependent on a high perception of risk; in one study, 62% of female patients attending a family planning clinic reported they would accept screening if it were offered to them, while 7% of patients felt they were at risk for HCV.[68]

Some studies found a positive association between HCV knowledge and willingness to accept screening, and that patients were encouraged to screen by elements of the screening process that enabled them to gather information.[58,65] For example, in one study of baby boomers attending a hospital emergency department (ED) a statistically significant association was reported between believing that carrying an HCV infection is likely permanent without treatment, or believing that people with HCV can look and feel fine, and acceptance of HCV screening.[58] Another study found that the use of an online HCV risk-assessment and test planning tool facilitated information gathering, which contributed to the decision to pursue testing.[65] Furthermore, in this study the information provided by the online tool itself was a sufficient motivator for some participants to proceed with HCV testing: "Well, it [the personal advice] is so clear that you feel compelled to follow the advice you receive."[65]

However, the level of knowledge about HCV may not always be associated with acceptance of screening. In one study, the acceptability of screening in a high risk urban population did not change after an educational intervention that significantly improved knowledge of HCV, as acceptance of screening was already high at baseline.[63] Interestingly, after receiving the educational intervention, these study participants thought that other members of their community would be more accepting of HCV testing and that those who tested positive would drink less alcohol.[63]

*People consider the implications for and availability of management for HCV when deliberating about screening.*

Study participants often considered the implications for and availability of management of HCV, including treatment and lifestyle advice, when deciding about screening. The desire to access early treatment was a motivator to seek HCV testing reported by the majority (66%) of participants in one study of PWID.[66] Interviewed participants in another study of users of an online risk assessment tool shared this view, further commenting that knowing about early treatment options and believing they are effective provides enough of a reason to get tested: "These diseases always start small. They are invisible and, later on, they develop further and, at a certain point, you're too late for treatment. You know, it gives you problems. If you find it at an early stage, you may be able to cure or treat it."[65]

Desire for treatment in general was also reported; the majority of participants from a study of a high risk urban population stated that they would want treatment if they tested positive for HCV (98%), that every HCV-positive

individual should be treated (76%), and that other HCV-positive members of their community would seek treatment (76%).[63] This study also found that, even in the absence of available treatment, the offer of healthy lifestyle advice for people who tested positive for HCV increased participant willingness to undergo screening from 90% to 96%.[63] Further, in another study, some members of a surveyed group of hospital outpatients felt strongly about the link between screening and treatment; six of 200 survey respondents commented that HCV testing should be a requirement to receive care.[64]

In some studies, when participants reported believing that they would not be able to access or benefit from treatment, some were less likely to accept HCV screening. For example, in one study, PWID in Sydney, Australia were surveyed about their reasons for delaying HCV screening: 12% agreed or strongly agreed that, "I could not afford treatment if I were infected" and 9% agreed or strongly agreed that, "I don't think that treatment makes a difference."[66] In another study, while 96% of individuals from a high risk urban population would personally accept screening with healthy lifestyle advice but without treatment, 49% of them thought that other members of their community would be in favour of screening without access to treatment (a perception that decreased after an HCV education session), or would drink less alcohol after a positive HCV test result.[63] In another study, some users of an online risk assessment tool reported delaying testing because they did not feel that immediate treatment for HCV was necessary: "It is not something that is life-threatening. It is not like if I don't get treated within a month, I will be dead by next month. You know, because it is such a long time ago."[65]

*Decisions about HCV screening are influenced by psychological and interpersonal contexts such as fear, embarrassment, denial, interest in personal health, concern for others, and relationships with others.*

**Fear of a positive test result and of disease**

Anxiety while waiting for test results[66] and fear of a positive result[61,66,67] were commonly reported reasons for participants in the included studies to decide against HCV screening or returning to receive results. For some, this extended to a fear of the events associated with a positive test result, complete with uncertain disease outcomes and treatment burdens. For example: "Is taking the medication hard? Are you stuck with it for the rest of your life? What is it? What are the risks? I don't have a clue. And imagine that the test result is positive. Then you think, "What am I getting myself into?'"[65] In one study of inmates, fear of testing was also reported and appeared to be related to limited knowledge about HCV risk factors, transmission, disease prognosis, and treatment.[67] For example: "Er, I don't know really; [pause] er, I don't really know. I mean, I think like I say, I think people are just frightened, ye na [you know]. People are frightened to get the test, ye na [you know], thinking that it could be a killer not knowing what, not knowing what it actually is, what it actually does to you, I mean?"[67]

**Denial of potential infection, and embarrassment to request screening**

In some studies, participants described a state of denial of potential HCV infection, and some people appear to have rejected HCV screening because they did not want to consider the possibility of infection or the negative psychological consequences of being infected.[61,65] For example: "I'm in denial. I don't want to hear that I have it."[61]

Embarrassment emerged as another reason people did not pursue HCV screening. In one study of PWID, 26% of participants who delayed HCV screening reported doing so because they were embarrassed to request screening,[66] and in another, a similar concern was reported in relation to concern about health care provider's perceptions: "I have a lot of health problems. Visits to the GP [general practitioner] are time-consuming and, above all, you don't want to be thought of as a whiner. [...] Every time you have something, you kind of start to dislike to yourself and, by bringing it up with the GP, it's like you are again making a big deal out of things."[65]

**Interest in personal health and concern for others**

Concern for others[61,64-68] and maintenance of one's own personal health[61,64,65,68] both emerged as relevant components in the decision to pursue HCV screening. Views about personal health in the context of HCV screening were limited to a vague concept of overall health. For example: "Knowing [my HCV status] is something that I need to do to stay healthy. Knowing that I'll feel better about myself if the results are good makes it easier to get tested."[61] Some participants connected these views about screening to a sense of personal responsibility for their health: "Look, when I hear about something like this, I take action immediately. It is my body and I believe that we should care for our bodies. And when you are offered something like this, well, then you should do it."[65]

In addition to concern for their own health, in several studies, participants reported valuing HCV screening as a way to ensure that they did not pass on an infection to their loved ones and the larger community.[61,64-68] As one participant stated, "if I knew I was positive, then I would take caution to not infect my family."[61] This sentiment was expressed across all study populations, although it was reported with varying frequencies in different groups; 74% of PWID in one study agreed that they had sought testing in the past in order to prevent transmission to others,[66] while 14% of women attending a sexual health and family planning clinic would accept screening to prevent putting others at risk, and 3% cited wanting to avoid passing HCV to their unborn child.[68]

**Relationship with health care providers, others, and society**

For some individuals, the decision regarding HCV screening was influenced by relationships with health care providers and the larger health care system, and also by the opinions and experiences of other people in their lives. For example, in one study a positive rapport with a doctor emerged as a factor that made testing easier,[61] and in another personally knowing someone who is experiencing health issues that may be related to HCV seemed to increase awareness and perceived importance of screening. For

example: “At this time, I have acquaintances who are dying because of their liver. So I think the liver is very important.”[65]

The potential impact on personal relationships and the influence of those individuals was also a reported deterrent to HCV screening. For example, 34% of PWID in one study reported that they delayed testing because they were “worried about [their] partner getting angry.”[66] Others described discouragement of testing coming directly from those close to them.[65]

A study of users of an online risk assessment tool raised the notion that some people might pursue screening for altruistic reasons; for example, in the interest of science or the organization conducting the testing.[65] In contrast, another study about acceptance of HCV screening in prison found that two participants were not willing to be tested because they did not “trust the government.”[69]

## Descriptive Theme 2

## People have preferences around and face barriers regarding the implementation of their decision to screen.

*Preferences around implementation of screening include views about consent and initiators of testing, clinical setting of screening, test methods, and delivery of test information and results.*

**Clinical setting of HCV screening**

Some preferences regarding the locations and types of clinical settings in which the testing was offered were elicited through participants’ descriptions of their experiences with HCV screening. For example, PWID who had accessed local syringe exchange programs and mobile testing units identified that these community-based testing locations facilitated HCV screening, and few of them experienced barriers to testing associated with this health care setting.[61] Similarly, another study of PWID found that participant preferences for HCV screening locations aligned with the location in which they had previously been tested for HCV (e.g., general practitioner’s office, methadone clinic, other specialized clinic), with the exception of participants who had previously been screened in prison.[66] However, 12% of participants in this study reported that they delayed testing because they did not want to go to a clinic.[66]

In some cases, participants who may not have expected or did not have prior experience with HCV screening indicated that they were deterred by HCV testing in a certain location or clinical setting. Two studies conducted in an ED found that some patients refused testing because they wanted to leave the ED,[58] and that 3% of participants strongly agreed that they were uncomfortable when offered HCV screening during triage.[60] However, 92% of ED patients were not uncomfortable with the offer of HCV screening in this setting.[60] One study took place at a family planning and sexual health clinic, where female patients were surveyed about their hypothetical acceptance of proposed HCV screening.[68] In this study, a small proportion indicated that they would rather receive this screening in a different clinical

setting, or that they would be offended if offered HCV screening at that clinic (2% and 4%, respectively).[68]

Other features of a clinical setting that were reported to facilitate HCV screening included settings that allowed for a sense of anonymity in and convenient access to the location of testing. Participants valued locations in which the test itself was confidential, but also where the atmosphere made patients feel comfortable and that they fit in with the other patients. For example, in relation to a community-based syringe exchange program, some participants who used injection drugs appreciated "having a safe environment where people aren't going to 'notice you,' such as here [syringe exchange program], where you know that other people are here for the same reason."[61] In another study where participants completed an online HCV risk assessment, and high-risk participants received advice to seek testing in the location of their choice, a similar preference is described. For example: "Where I live — a small village — if you [go] to the local care unit where blood is drawn, you see all sorts of people you know. If you sit there, then you're either pregnant or you have some scary disease. Well for me, I don't like that, so I'd prefer to go to Amsterdam."[65] In this study, the online risk assessment tool was preferred by some because it enabled testing that remained confidential from participants' doctors, as well: "At that time [years ago], I thought about testing, but I didn't do it. [...] The reason is that, back then, you had to visit the GP — it was the standard procedure — and you'd have to tell him or her why you want a test [...] and, with this offer, you can remain anonymous but still get tested."[65] Other participants from this study felt that the operational features at the labs that offered testing (e.g., limited business hours and necessity for appointments) were too inconvenient for them to undergo the advised HCV screening.[65]

**Initiators of testing and consent**

Another preference that emerged relates to not having to take the initiative to get tested, as this was seen to make HCV screening decisions easier to implement. Some participants in the included studies discussed preferences for screening processes that contained scheduling tools and reminders, and likewise described these as facilitators of testing: "Well, actually, I think if I didn't get that reminder of yours, it would have ended up in the back of my mind, like something I would have to do some time. [...] Without the reminder, I probably wouldn't have gotten tested."[65] Some participants from another study of PWID similarly favoured a routine offer of HCV screening: "When it's [HCV testing] offered to me on a regular basis [it makes it easier to get tested]."[61] Beyond a routine offer of HCV screening, most participants in one study that included outpatients at an urban hospital[64] felt that the blood of all hospital patients should automatically be tested for HCV. In this study, discussion of automatic testing was closely linked to participants' values of knowing about and consenting to blood tests, and of receiving test results. A majority of participants in this study said that it was important to know about the tests being done on their blood, that they would like to know about the testing before it was conducted, and that they would like to receive any result (i.e., not only hear about positive results). However, when ranking their preferences, most patients indicated that they would rather have universal, automatic testing without their knowledge or without receiving

negative test results than not be tested at all. Fewer patients preferred the screening option initiated by clinician judgment.[64]

**Delivery of test information and results**

Participants who had experience with HCV screening described various ways in which information about the test itself and test results were provided, and how that affected their experience. Given the sensitive nature of HCV testing and the potential fear around test results, participants in several studies expressed a preference to discuss HCV testing with a health care professional. For example, PWID in one study preferred an in-person discussion with a nurse or counsellor (59%) to reading written materials (22%) about HCV testing and management prior to having the test.[66] More participants in this study reported also preferring to receive test results in person (80%) rather than over the phone (18%).[66] However, 15% of participants in this study reported delayed testing because they did not want to speak with a counsellor.[66] People may not hold the preference that test results be delivered by the same clinical team that administered the test. For example, 75% of hospital outpatients in one study indicated that they would accept the delivery of results of a hospital HCV test from a member of the public health department as opposed to hospital staff.[64] What seems to be of the most importance is that the conversation around HCV testing and results is of appropriate quality and depth from the perspective of the person being tested.[67]

Finally, one study that evaluated the choice of HCV test methods in young PWID found that timing of test result delivery factored heavily in their decision to pursue screening. Of those participants that chose a rapid test, 60% did so because they wanted fast results and most of those preferred same-day results. Likewise, 14% of participants who chose the standard blood test did so because they did not want test results that day.[62]

**Test method and blood sampling**

Two included studies examined participant views and preferences for HCV screening methods and both found that many participants favoured alternatives to the standard blood test. In one study, 83% of participants chose an HCV rapid test over the standard blood test because they wanted results quickly.[62] Significantly more participants in a birth cohort study reported they would agree to a saliva-based test (89.4%) over a blood test (85.4%; $P = 0.009$), although the reasons behind this choice were not investigated.[59] Other reasons for the choice of a rapid test versus a blood test emerged and were based on personal experiences of pain or discomfort, or perceptions of test accuracy and reliability. The majority of people who chose the rapid test in one study felt that it was not more painful or less accurate than the standard blood test,[62] while others wanted to avoid the rapid test because of the associated finger prick[58,62] or because of a sense that the standard blood test was more trustworthy.[62]

It appears that, for people with a history of IDU, some preferences about the HCV test method are connected to the process of drawing blood. In two studies, some participants indicated that they delayed screening to avoid having their blood drawn, or that they would prefer to draw their own blood,

often because of the difficulty that phlebotomists can have accessing their veins.[66,67]

**Other barriers and facilitators to HCV screening**

Other various barriers and facilitators to implementing the decision to pursue screening also emerged. For example, in one study some participants reported that HCV screening was perceived as a low priority because they did not feel unwell and others described events in their lives that took precedence over HCV testing at the time, regardless of their willingness or intent to be screened.[65] Life events that took precedence included such things as attending to a hospitalized parent,[65] experiencing drug and alcohol withdrawal,[67] and prioritizing other blood tests for the management of existing health conditions.[65]

Additional reported facilitators and barriers to HCV screening included: awareness of testing locations,[61,66,67] the perceived convenience of the test,[62,65,66] having or lacking time to get screened,[61] and the cost of the screening test.[61,63,64,66]

*PWID and incarcerated individuals experience unique barriers to HCV screening related to stigma and access to health care.*

**Stigma associated with HCV and IDU**

Stigma was a barrier to HCV screening that emerged within studies that included PWID, including stigma associated with IDU and with HCV.[61,66,67] Half of participants in one study reported delaying HCV screening because they were concerned that they would be treated differently if they were found to have HCV.[66] A participant in another study of inmates with a history of IDU reported witnessing such negative treatment of an HCV-positive fellow inmate: “There was a lass with hep C on Landing 2 and it was "Heppie" and that they call her, do you know what I mean? Yeah. Not very nice.”[67] Participants in these studies also noted that HCV infection did not have to be confirmed in order for PWID to suffer from stigma: “People know that most of the time you get tested for hep C because you’re an IV user. People judge you no matter what your results are. That’s the worst feeling ever.”[61] In one study, participants seemed to link this judgment to a public perception that PWID are responsible for their HCV infections, which led to a belief that treatment would subsequently be limited for these individuals.[67]

When stigma was identified as a concern regarding HCV screening, it was often accompanied by concerns about confidentiality and who would be able to access test results. In a survey study of PWID, 14% of surveyed participants said that they delayed testing because they could not be tested anonymously, while 28% attributed the delay to a fear of their name being reported if they tested positive for HCV.[66] In another qualitative study of inmates with a history of IDU, people described the lack of confidentiality among other inmates and prison staff as a deterrent to seeking testing. In particular, the bruising resulting from failed attempts at venipuncture was reported to bring attention toward people who have been screened and result in stigmatization.[67]

### Access to health care and HCV screening

Access to health care and HCV screening was another issue that emerged in studies of marginalized and vulnerable populations, such as PWID and inmates in correctional facilities.[61,67] In one study that surveyed PWID, having regular access to a health care provider and transportation were reported facilitators to HCV screening; likewise, lacking these things were reported barriers to screening.[61] In another study in which inmates were interviewed regarding their uptake of HCV screening, some participants perceived that they did not have the same access to health care in prison that they would otherwise.[67] While a direct link to HCV screening was not necessarily articulated, this perception of limited access to care reflects the context in which some inmates would make any health care decision.

Reduced access to health care among PWID and inmates may also be related to the transient lifestyle commonly associated with these groups. For example, in one study, 64% of PWID attributed their delay in testing to a difficulty keeping appointments.[66] Further, participants also reported moving away and being discharged from prison or drug treatment facilities as factors that interfered with HCV testing and receiving results.[66,67] A participant in one study described the lack of continuity of care between the community and prison as a barrier to the completion of planned HCV screening: "They gave us a vaccination, then gave us another one, then I got me booster, but in the meantime while I was still using they wanted to take me blood afterwards to make sure if I had caught anything in the meantime. (Yeah.) But I ended up in prison. (Right.) So I couldn't get me blood taken."[67] Finally, it appears that prison presents specific institutional barriers to screening that members of the general population would not face, such as applications to receive blood tests, which appear to deter people from screening.[67]

## Research question 5 — Clinical validity

### Study characteristics

#### *Study Design and Setting*

A total of 26 studies[24,70-94] were included for this research question. The majority were cross-sectional prevalence studies, while two studies were cross-sectional studies focused on assay development and evaluation.[24,90] The studies were conducted in Italy,[24,72,73,88,89,91,93] the US,[70,79,90] Brazil,[74,78,83] Turkey,[80,97] the Netherlands,[84,94] Sweden,[71] Poland,[85] Norway,[86] Greece,[87] Morocco,[75] Burkina Faso,[76] China,[77] Jordan,[82] and the Solomon Islands.[92] Eleven studies were conducted in blood banks or hospital transfusion centres.[24,72-74,76,82,85,87,90,92,94] Five studies were conducted in other hospital departments[70,80,98] or outpatient clinic-based settings,[71,84] while the remaining ten studies used a population-based sampling approach to recruit participants from a community setting.[75,77-79,83,86,88,89,91,93]

### *Funding and Conflicts of Interest*

Lyons et al.,[70] Woo et al.,[79] Slavenburg et al.,[84] Letowska et al.,[85] and Dalgard et al.[86] received study funding or other contributions at least in part from pharmaceutical companies. Sources of funding for the other studies included institutional support and government grants,[71,74,77,78,88,89,91,93] while Sommese et al.[72] reported that they did not receive any funding. Sources of funding were not reported by 12 studies.[24,73,75,76,80-83,87,90,92,94] The authors of eight studies declared no conflict of interest,[71,72,74-78,81] while Lyons et al.[70] reported that the authors received support and research grants from industry, and served on pharmaceutical advisory and data safety monitoring boards. Most study authors did not report on potential conflicts of interest.[24,73,79,80,82-94]

### *Screening Test*

**Ab tests**

Twenty-three studies used a third-generation HCV Ab test as the initial screening test.[70-84,86-89,91-94] The Ab tests evaluated in the included studies were as follows:

- Ortho HCV version 3.0 ELISA[86,88,89,91-94]
- ARCHITECT anti-HCV CMIA[71,72,76,80,81]
- VITROS anti-HCV CLIA[78,79]
- Cobas e411 anti-HCV electrochemiluminescent immunoassay (ECLIA)[72] and the Cobas e601 anti-HCV ECLIA[81]
- Murex anti-HCV version 4.0 ELISA[74,75] and another third-generation Murex anti-HCV ELISA, not otherwise specified[87]
- BioChain anti-HCV ELISA[70]
- Wantai Core anti-HCV ELISA[77]
- Kehua Core anti-HCV ELISA[77]
- DiaSorin anti-HCV ELISA[82]
- INNOTEST HCV Ab III ELISA[83]
- Bioelisa HCV 4.0 ELISA[84]
- AxSYM HCV MEIA (as a secondary Ab test only)[75,84]
- Bio-Rad ELISA (as a secondary Ab test only).[76]

Seventeen studies evaluated screening using single Ab assays,[70,71,73,74,78-80,82,83,86-89,91-94] while two studies included multiple unique Ab assays in their study, each assay assessed independently of the others.[72,81] Baha et al.,[75] Zeba et al.,[76] and Slavenburg et al.[84] investigated an Ab testing pathway approach, where only samples that were reactive on the first Ab test would progress to a second, different Ab test. Subsequently, Slavenburg et al.[84] also required confirmation of Ab-reactivity on the INNO-LIA immunoblot test for samples to continue on to PCR testing. Li et al.[77] evaluated combination Ab testing, where samples were considered Ab-positive if reactive on both

the Wantai Core and Kehua Core anti-HCV ELISAs, although an order of testing was not reported.

When reported, samples were considered Ab-positive when repeatedly reactive on the Ab test,[87,88,94] and with or without confirmation on the INNO-LIA immunoblot test.[72,73,83] Of the three studies that mention sample repeat reactivity in the methods, initially positive samples were considered repeatedly reactive if positive upon retesting in duplicate in one study[87] or positive upon retesting within one month (number of replicates not reported) in another;[88] however, this term was not described in the study by Vrielink et al.[94] Some studies specified a signal–to–cut-off ratio of 1.0 or greater for classifying samples as Ab-positive,[72,73,79,84] and/or reported that the Ab assays were performed according to the manufacturer's instructions.[72,73,80-82,89,91,93].

**Ag tests**

Four studies evaluated an HCV Ag test[24,80,85,90] including:

- Ortho HCV Core Ag ELISA[24,85]
- ARCHITECT HCV Ag CMIA[80]
- PRISM HCV Core Ag CLIA.[90]

Three studies reported a cut-off value for Ag-reactivity,[24,80,90] while Letowska et al.[85] reported that the test was performed according to the manufacturer's instructions. Three studies reported that repeatedly reactive samples were considered Ag-positive.[24,80,85] In the study by Kesli et al.,[80] initially reactive samples were retested in duplicate and considered to be Ag-positive if one or both of the duplicates were also reactive. In the study by Icardi et al.,[24] initially reactive samples that were still positive at retesting were considered Ag-positive, although the method for retesting was not described. Letowska et al.[85] did not define "repeatedly reactive" for their study.

*Diagnostic Test*

For the PCR test to detect HCV-RNA, 17 studies reported the use of a commercial assay or test system,[24,70-73,75-81,84,85,88,89,92] the most common of which was the Cobas Amplicor test manufactured by Roche.[24,75,78,85,89,92] Four studies described a reverse transcription PCR test using primers complementary to the conserved area of the 5' untranslated region of HCV,[74,83,91,93] while Zervou et al.[87] used a combined reverse transcription PCR (RT-PCR) and DNA enzyme immunoassay approach to detect RNA. A limit of detection or assay sensitivity for the PCR test was provided in 14 studies,[24,70,72,73,75,78,80,81,84,86,87,89-91] (see Table 10 for details) and Muerhoff et al.[90] defined a PCR-positive result as the presence of a DNA fragment of the expected size in the test sample but not in any of the negative controls. Four studies did not provide detailed descriptions of their PCR test or methods.[82,86,90,94]

In the studies by Lyons et al.[70] and Kesli et al.,[80] all samples were tested for HCV-RNA by PCR, irrespective of their result on the screening test. In all other studies, only positive samples on the screening test proceeded to PCR testing, although the definitions of screening test-positivity were study-

specific and varied regarding requirements for repeat reactivity on the initial assay, confirmation with a supplementary immunoblot, and subsequent testing with additional assays.

*Interval Between Screening and Diagnostic Tests*

Most studies (n = 22) appeared to use a single blood or serum sample for all tests; however, recall or repeat testing was performed in four studies.[75,86,88,94] Alberti et al.[88] repeated Ab testing on initially reactive samples within one month, and confirmed Ab-positive serum was tested for RNA by PCR. Then, initially RNA-negative samples were retested by PCR at one and three months. In two studies, Ab-positive patients were recalled at a subsequent date to provide a fresh blood sample for PCR testing; however, the interval between sampling for each test was not reported.[75,94] Dalgard et al.[86] defined HCV-RNA negativity as "at least three negative and no positive PCR tests within 12 months," but it is unclear whether this was based on a retrospective review of the patients' medical record or prospective repeated sampling for the study.

Additional details regarding study characteristics can be found in Table 10 in Appendix 6.

**Patient characteristics**

The patient population consisted of blood donors in 10 studies,[72-74,76,82,85,87,90,92,94] members of the general population in 10 studies (including one study by Martins et al.[78] that exclusively included elderly patients),[75,77-79,83,86,88,89,91,93] and one study included both.[24] The remaining five studies recruited patients from various health care settings.[70,71,80,81,84] Lyons et al.[70] selected adults in an urban ED; Blaxhult et al.[71] included HIV-negative men, who have sex with men, attending a sexually transmitted infection (STI) clinic; both studies by Kesli et al.[80,81] selected patients at low-risk for HCV infection who were referred to a hospital microbiology department for unspecified reasons; and Slavenburg et al.[84] screened "leftover" blood samples from patients who had been referred to a laboratory for blood analysis of biochemical parameters. The clinical status of the patients was not reported in this study; however, the fact that surplus blood samples were used in the study suggests that HCV testing was not the primary reason for the requisitioned blood test and it may be reasonable to assume that these patients were not suspected to have HCV infection.

Six studies explicitly stated that included patients were healthy or asymptomatic,[73,75,76,82,87,88] two studies included patients who were at low risk for HCV infection,[80,81] and one study reported that none of the included patients had a known HCV infection.[71] However, 17 studies did not base selection on clinical status,[24,70,72,74,77-79,83-86,89-94] so they may have included some patients with signs, symptoms, or risk factors for HCV, as well as those with a known HCV infection. The number and proportion of total included patients with known risk factors for HCV (e.g., history of IDU, HIV infection, transfusion prior to universal blood donation screening) or known HCV infection were reported in seven studies;[70,76,78,79,83,86,92] in all cases, these groups represented less than 20% of the total study population. Some studies did not restrict patient selection because one of the objectives was to

identify risk factors for HCV infection through univariate analysis or multiple logistic regression analysis.[74,75,77,91,93]

Additional details regarding patient characteristics can be found in Table 13 in Appendix 7.

## Risk of bias assessment

### *Patient Selection*

Most studies (n = 17) were determined to have a low risk of bias for patient selection by including random or consecutive samples and by avoiding inappropriate exclusions, as selection criteria were generally broad; however, there was an unclear risk of bias in seven studies because of a lack of detail regarding patient identification and selection methods,[24,72,73,80,81,83,84] and a high risk of bias in two studies.[79,89] While HCV screening was provided to any willing volunteers attending a cultural fair in the study by Woo et al.,[79] a particular focus was placed on offering screening to individuals with visible tattoos and those from Thailand, Vietnam, and Laos, as they were believed to be at a higher risk of having an HCV infection. This approach could have skewed the patient population to increase the prevalence of HCV infection above what would otherwise be expected among attendees at the fair, and potentially overestimate the number of screening test-positive individuals. However, this was not observed in the study results, as one of 231 screened individuals were Ab-positive — which is a result that may have been more affected by the study sample size than the recruitment strategy. Additionally, as these particular factors were not identified as critical HCV risk factors to be excluded from this review, this selection method did not present an applicability concern. In the study by Kondili et al.,[89] patients were approached several years after initial recruitment and HCV Ab testing for a second Ab test (the first RNA test was performed at this time); those who agreed to provide a second blood sample may have been systematically different than the entire study population at enrollment, which may influence the results but direction of the potential bias is unclear. This also presents an applicability concern, as repeated screening after several years to determine HCV incidence may not reflect the screening strategy of interest for this review.

It was unclear whether there were applicability concerns with the patient selection in three studies.[80,83,84] Reis et al.[83] included some children in the study; while the reported mean and median ages were greater than 18 years, it cannot be confirmed whether the study population was at least 80% adults, which is the population of interest for this review. Slavenburg et al.[84] included leftover blood samples from patients with unspecified clinical conditions referred for laboratory blood analysis. Although it may be inferred that HCV testing was not the primary reason for blood testing and therefore HCV infection was not suspected, it was not clear that these patients were asymptomatic. Similarly, Kesli et al.[80] tested serum samples from patients “at low risk for Hepatis C virus infection” referred to a hospital microbiology department; however, the majority of included patients had active HCV infection (as indicated by a positive result on an RNA test). This suggests that the description of the study population may have been inaccurate and

therefore may not be applicable to the low-risk, asymptomatic general population for a screening program of interest for this review. There was a high applicability concern for the study by Lucas and Faoagali,[92] which was conducted in a tropical, malaria-endemic country where there may be a high false-positive rate on HCV EIAs due to hyperglobulinemia; the screening test results obtained in this study likely do not reflect how the same test would perform in a country like Canada that is not endemic for malaria. The rest of the studies did not present major patient selection applicability concerns, although it was noted when studies focused on specific subsets of the general population[71,78] or broadly included individuals from the general population — which may have included some patients with HCV signs, symptoms, risk factors, or known HCV infection.[70,77,78,83,86,91,93]

### *Screening Test*

There was a low risk of bias regarding the screening test in 11 studies, which either described methods for the conduct and interpretation of the assay, or reported that the assays were performed according to the manufacturer's instructions.[24,72,73,79-82,85,89,91,93] Insufficient details regarding the screening test methods were provided to determine risk of bias in 14 studies.[70,71,74-78,83,84,86-88,92,94] The study by Muerhoff et al.[90] had a high risk of bias related to the screening test because a threshold was not pre-specified. Results were reported at a provisional cut-off designed to give as few positive results as possible, since blood donors were assumed to be Ag-negative; this may have overestimated test performance. It is also unclear whether the provisional cut-off used in this study is standard or currently recommended for this assay; if not, the results may not be generalizable to how this assay would perform in a general screening population in clinical practice. None of the other studies presented applicability concerns related to the screening test.

### *Diagnostic Test*

There was a low risk of bias regarding the diagnostic test in 17 studies, which either described methods for the conduct and interpretation of the assay, or reported that the assays were performed according to the manufacturer's instructions.[24,70,72,73,75-78,80,81,83,84,86,87,89-91] Insufficient details regarding the diagnostic test methods were provided to determine risk of bias in nine studies.[71,74,79,82,85,88,92-94] None of the studies had a high risk of bias or applicability concerns related to the diagnostic test.

### *Flow and Timing*

Most studies (n = 22) were at a low risk of bias because of the flow and timing of screening and diagnostic testing, as they appeared to use a single blood or serum sample for all tests and therefore there was no interval between Ab or Ag and RNA testing.[24,70-74,76-85,87,89-93] Recall or repeat testing was performed in four studies[75,86,88,94] — two of which defined intervals within which PCR testing was performed and within which it is unlikely that chronic viral infection status would have changed — suggesting a low risk of bias.[86,88] In two studies, Ab-positive patients were recalled at a subsequent date to provide a fresh blood sample for PCR testing; however, the interval between sampling for each test was not reported.[75,94] It is unclear whether

this interval was the same for all patients or whether it could have affected the results on the diagnostic test. The risk of bias for these two studies is therefore unclear.

All samples, irrespective of the result on the screening test, were evaluated with both the screening test and the diagnostic test in two studies, indicating a low risk of bias.[70,80] In the remaining 24 studies, only Ab-positive or Ag-positive samples (according to the study-specific definition of screening test-positivity) progressed to PCR testing; however, this did not necessarily bias the results that were reported, as these studies did not attempt to extrapolate conclusions regarding Ab-negative patients or Ag-negative patients. All patients in each included study received the same diagnostic test and none of the studies lost patients to follow-up. Martins et al.[78] excluded 73 patients from the analysis who participated in a health assessment interview but did not provide a blood sample; however, the patient characteristics and history of risk factors were not found to be significantly different between the included and excluded patients, so this was not judged to increase the risk of bias for this study.

Additional details regarding risk of bias assessments can be found in Table 16 in Appendix 8.

## Data analysis and synthesis

Because of the heterogeneity in the screening tests used and study populations included in the identified studies, a meta-analysis of the screening effectiveness of Ab and Ag tests was not conducted. Of the 26 included studies, 23 reported on HCV Ab tests[70-84,86-89,91-94] and four reported on HCV Ag tests.[24,80,85,90]

Additional Ab test results and Ag test results for each included study, including the number of patients tested overall and the number of positive patients, are presented in Table 20 and Table 21 respectively, in Appendix 9.

### *Ab Tests*

**Ab+RNA+ (of all Ab+)**

The proportion of HCV Ab-positive patients identified by screening with the HCV Ab test who also were shown to have active viral infection by PCR was evaluated in 23 studies; this value ranged overall from 0% in three studies (Ortho HCV version 3.0 ELISA for blood donors in the Solomon Islands,[92] VITROS Anti-HCV CLIA to screen attendees at a community fair,[79] and INNOTEST HCV Ab III ELISA to screen members of the general population in Brazil[83]) to 89.7% in one study (DiaSorin anti-HCV ELISA, third generation for blood donors in Jordan[82]).

Laboratory directors for four of five provinces who responded to CADTH's informal query regarding screening test usage indicated that the Abbott ARCHITECT anti-HCV CMIA is used in their provincial public health laboratories for the purpose of hepatitis C screening (Dr. Jordan Feld, Toronto General Hospital Liver Centre, University Health Network, McLaughlin-Rotman Centre for Global Health, Toronto: ON: personal

communication, 2016 Dec). Studies that evaluated this screening test in blood donors and clinical samples also reported a wide range of results; using the ARCHITECTanti-HCV CMIA, the proportion of Ab-positive patients who also tested positive for HCV-RNA ranged from 10.1% to 38.9% in blood donors and 33.3% to 80.3% in clinic samples.

These results are presented for each test, by population studied, in Table 3.

### Table 3: Proportion of Ab-Positive Patients With Active Viral Infection by PCR (Ab+RNA+/Ab+)

| Ab Test | General Population | Blood Donors | Clinic Samples |
|---|---|---|---|
| Ortho HCV version 3.0 ELISA | 5 studies:<br>• 43/92 = 46.7%[91]<br>• 62/86 = 72.1%[86]<br>• 85/116 = 73.3%[88]<br>• 148/195 = 75.9%[93]<br>• 28/32 = 87.5%[89] | 2 studies:<br>• 0/36 = 0%92<br>• 15/387 = 3.9%94 | NA |
| ARCHITECT Anti-HCV CMIA | NA | 3 studies (including 1 study with 2 parts):<br>• 9/89 = 10.1%[73]<br>• 7/25 = 28.0%[72]<br>• 32/97 = 33.0%[76a]<br>• 7/18 = 38.9%[72b] | 3 studies:<br>• 2/6 = 33.3%[71]<br>• 65/86 = 75.6%[81]<br>• 155/193 = 80.3%[80] |
| VITROS Anti-HCV CLIA | 2 studies:<br>• 0/1 = 0%[79]<br>• 14/18 = 77.8%[78] | NA | NA |
| Cobas e411 Anti-HCV ECLIA | NA | 1 study, 2 parts:<br>• 7/19 = 36.8%[72]<br>• 7/17 = 41.2%[72c] | NA |
| Cobas e601 Anti-HCV ECLIA | NA | NA | 1 study:<br>• 65/136 = 47.8%[81] |
| Murex Anti-HCV version 4.0 ELISA | 1 study:<br>• 462/651 = 71.0%[75d] | 1 study:<br>• 106/146 = 72.6%[74] | NA |
| Murex Anti-HCV ELISA, third generation | NA | 1 study:<br>• 7/41 = 17.1%[87] | NA |
| Biochain Anti-HCV ELISA | NA | NA | 1 study:<br>• 103/128 = 80.5%[70] |
| Wantai Core Anti-HCV ELISA and Kehua Core Anti-HCV ELISA, third generation | 1 study:<br>• 44/118 = 37.3%[77] | NA | NA |
| DiaSorin Anti-HCV ELISA, third generation | NA | 1 study:<br>• 26/29 = 89.7%[82] | NA |
| INNOTEST HCV Ab III ELISA | 1 study, 2 parts:<br>• 0/6 = 0%[83]<br>• 0/2 = 0%[83c] | NA | NA |

### Table 3: Proportion of Ab-Positive Patients With Active Viral Infection by PCR (Ab+RNA+/Ab+)

| Ab Test | General Population | Blood Donors | Clinic Samples |
|---|---|---|---|
| Bioelisa HCV 4.0 ELISA, AxSYM HCV version 3.0 MEIA, and INNO-LIA immunoblot | NA | NA | 1 study:<br>• 2/4 = 50.0%[84] |

Ab = antibody; CLIA = chemiluminescent immunoassay; CMIA = chemiluminescent microparticle immunoassay; ECLIA = electrochemiluminescent immunoassay; ELISA = enzyme-linked immunosorbent assay; HCV = hepatitis C virus; MEIA = microparticle enzyme immunoassay; NA = not applicable; PCR = polymerase chain reaction; RNA = ribonucleic acid.
[a] Value reflects samples reactive on both the initial screening test (ARCHITECT) and the second Ab test (Bio-Rad ELISA).
[b] Value reflects samples with INNO-LIA confirmation; value for repeatedly reactive samples on ARCHITECT alone was 28.0%.[72]
[c] First value (larger denominator) reflects repeatedly reactive samples on Ab test alone, second value (smaller denominator) reflects samples with INNO-LIA confirmation.
[d] Value reflects samples reactive on both the initial screening test (Murex) and the second Ab test (AxSYM HCV MEIA).

Two studies[72,83] reported results separately for samples found to be Ab-positive by the screening tests alone and for reactive samples that were confirmed to be Ab-positive by INNO-LIA immunoblot. For all three screening tests (ARCHITECT Anti-HCV CMIA or Cobas e411 Anti-HCV ECLIA[72] and INNOTEST HCV Ab III ELISA[83]), the number of Ab-positive samples decreased when confirmed by immunoblot; this increased the proportion of Ab-positive patients with active viral infection for one study[72] but not the other, which did not identify any RNA-positive patients.[83]

The wide range of results observed across studies may reflect differences in test performance but may also be influenced by several study variables, such as population characteristics. In general, the proportions of Ab-positive individuals with active infection were higher (> 70%) in studies conducted on a general population[75,78,86,88,89,93] and lower (< 40%) in studies conducted with blood donor samples.[72,73,76,87,92,94] This may be attributed to the pre-screening questionnaires and assessments that are applied to screen out high-risk potential blood donors before a blood sample is obtained. However, there may also be other population factors that influence test performance. Two studies that tested blood donor samples with the Ortho HCV version 3.0 ELISA[92,94] demonstrated dramatically lower proportions of Ab+RNA+ results of all Ab+ samples than studies using the same test to screen samples from the general population (see Table 3). The study by Lucas and Faoagali[92] showed that none of the 36 Ab+ samples were RNA+. However, three of the 36 Ab+ samples were confirmed to be reactive for anti-HCV Ab by the recombinant immunoblot assay (RIBA), suggesting that the majority of Ab+ samples were false-positives. This study was conducted in the Soloman Islands, an area endemic for malaria, which may result in a high false-positive anti-HCV rate on third-generation EIAs.[92] Similarly, the second study by Vrielink et al.[94] showed that 15 of 387 Ab+ samples from European blood donors were also RNA+; again, most of these samples were likely false-positive for Ab, as 369 of the Ab+ samples were either RIBA-negative or indeterminate. In this study, none of the RIBA+ individuals presented risk factors for HCV, suggesting that these results may reflect Ortho HCV version 3.0 ELISA performance in a low-risk blood donor

population. Variability in population characteristics may also contribute to the variation in results seen for studies using clinical samples, as this was a broad category that consisted of many different types of patients in various clinical settings, including general practices,[84] hospital microbiology departments,[80,81] clinics for STI testing,[71] and an emergency deparment.[70]

Another factor that may affect the results is sample size; a study with a small sample size in a low-prevalence population may be insufficient to detect enough Ab+ individuals to provide an accurate representation of those individuals with active viremia. For example, the studies that did not identify any Ab+RNA+ individuals among all Ab+ samples had sample sizes of 598,[92] 231,[79] and 1,007.[83] However, 13 studies had sample sizes of at least 2,000,[73-77,81,82,84,86-89,94] and the proportion of Ab+RNA+ individuals among all Ab+ people in these studies ranged from 3.9% to 89.7%; this suggests that there are factors other than study sample size affecting this outcome. Beyond total study sample size, six studies identified fewer than 20 Ab+ samples in the entire study population, and the proportion of viremic patients was generally low in these studies (0%,[79,83] 33.3%,[71] 38.9%,[72] 50.0%,[84] and 77.8%[78]). Therefore, the precision and reliability of results provided by studies with a small number of Ab+ samples is limited and strong conclusions may not be drawn from these studies. However, excluding these studies from the analysis does not alter the range of results observed for these studies; this observation supports the conclusion that there are several variables contributing to the results, and that a primary driver of the results was not identified.

There are likely other sources of variability that remain unclear, as several Ab tests or combinations of tests were evaluated in one study each.[70,72,74,75,77,81-84,87]

Overall, based on results reported by studies with a large sample size (n > 1,000) in a general population (i.e., in contrast to blood donors who are likely pre-screened), Ab tests appear to be moderately good at identifying individuals with active HCV infection, as the proportion of Ab-positive individuals with HCV viremia ranged from 71.0% to 87.5% in these five studies.[75,86,88,89,93] In a screening scenario, this would mean that up to 29% of Ab-positive people would unnecessarily proceed to RNA testing. This may be acceptable for the first step in a screening pathway, since the main goal is to avoid missing cases (screening in is more important than screening out), and there are few harms associated with a non-invasive diagnostic test like PCR.

**Ab–RNA– (of all Ab–)**

The proportion of Ab-negative patients who were confirmed not to have active viral infection by PCR was evaluated in two studies;[70,80] the majority of studies (n = 24) did not perform PCR testing in Ab-negative samples, so this outcome was not frequently reported. In patients referred to a hospital microbiology department in Turkey who were screened for HCV Abs with the ARCHITECT Anti-HCV CMIA, 73.7% of Ab-negative patients were shown to be virus-free by RT-PCR, and 26.3% of Ab-negative patients were RNA-positive.[80] However, the majority of the 212 patients in this study tested positive for both Ab (n = 193) and RNA (n = 160), suggesting that the study

population was not accurately described as “patients at low risk for hepatitis C virus”[80] and likely does not truly reflect a general screening population; this reduces the reliability and applicability of the study results for this review. Another screening study conducted in an urban ED in the US, in which patients were approached consecutively during the study periods, found that 99.7% of patients who were Ab-negative on the BioChain Anti-HCV ELISA were also RNA-negative by RT-PCR.[70]

*Ag Tests*

**Ag+RNA+ (of all Ag+)**

The proportion of HCV Ag-positive patients identified by screening with the HCV Ag test who also were shown to have active viral infection by PCR was evaluated in four studies,[24,80,85,90] but the validity of results was generally limited by the methods of patient selection[80] and the low number or absence of patients who tested positive for HCV Ag.[24,90] One study did not identify any Ag-positive patients among 500 tested (i.e., no samples progressed to RNA testing),[24] and another study identified one Ag-positive individual of 1,004 tested (i.e., one sample progressed to RNA testing); this patient was RNA-negative, giving a 0% result for the proportion of Ag+RNA+ individuals of all Ag-positive patients.[90] Likewise, one study found that 100% of Ag-positive blood donors were also RNA-positive, but two of 2,586 blood donors overall tested Ag-positive (i.e., two samples progressed to RNA testing and both were RNA-positive).[24] The remaining two studies reported that 20.2%[85] and 100%[80] of Ag-positive patients also tested RNA-positive. These results are presented for each test, by population studied, in Table 4.

## Table 4: Proportion of Ag-Positive Patients With Active Viral Infection By PCR (Ag+RNA+/Ag+)

| Ag Test | General Population | Blood Donors | Clinic Samples |
|---|---|---|---|
| ARCHITECT HCV Antigen CMIA | NA | NA | 1 study:<br>• 154/154 = 100%[80] |
| PRISM HCV Core Antigen CLIA | NA | 1 study:<br>• 0/1 = 0%[90] | NA |
| Ortho HCV Core Antigen ELISA | 1 study:<br>• 0/0 = Not evaluable[24] | 2 studies:<br>• 25/124 = 20.2%[85]<br>• 2/2 = 100%[24] | NA |

Ag = antigen; CLIA = chemiluminescent immunoassay; CMIA = chemiluminescent microparticle immunoassay; ELISA = enzyme-linked immunosorbent assay; HCV = hepatitis C virus; NA = not applicable; PCR = polymerase chain reaction.

As with the results observed for the Ab tests, the results observed for each Ag test may not be entirely representative of test performance, and the discrepancy between the results reported by each of the included studies may have been affected by other sources of variation. The 0% or 100% proportion of Ag+RNA+ of all Ag-positive blood donors reported by Muerhoff et al.[90] and Icardi et al.,[24] respectively, is likely unreliable because of the limited number of Ag-positive samples identified in those studies. One patient of 1,004 tested was Ag-positive in the study by Muerhoff et al.,[90] and two of 2,586 samples tested Ag-positive in the study by Icardi et al.[24] The other study by Kesli et al.[80] evaluated the ARCHITECT HCV Ag CMIA, which laboratory directors have indicated is the Ag test used as part of the

hepatitis C screening pathway in two of five Canadian public health laboratories from which CADTH was able to receive a response (Dr. Jordan Feld: personal communication, 2016 Dec). This study was conducted using surplus blood samples from a hospital microbiology lab. Of the 212 samples screened, 154 were Ag-positive, and 100% of the Ag-positive samples were also RNA-positive. The patient samples were not well-described in the study, so it is unclear whether there were patient characteristics (such as suspected HCV infection) that could explain the high number of Ag-positive samples. Letowska et al.[85] screened a large number of blood donor samples (n = 133,279) for Ag, so it is possible that the 20.2% reported in this study is a more reliable value than the 0% or 100% results reported in the other three studies. Still, this proportion is lower than what would be expected, given that both Ag and RNA are indicators of active infection and therefore should correlate well with each other. This study was published in 2004 and evaluates the Ortho HCV Core Antigen ELISA test, which is not listed in the Health Canada Medical Devices Active License Listing; this suggests that the results of this study may not be current or applicable to a Canadian health care setting.

**Ag–RNA– (of all Ag–)**

Ag-negative samples were tested by PCR to investigate the presence of RNA in one study; Kesli et al.[80] reported that 89.7% of Ag-negative patients were confirmed not to have active viral infection by PCR. All of the Ag-negative samples that tested RNA-positive (n = 6) were categorized as having an RNA titre lower than $10^5$ IU/mL; it is possible that the amount of virus in the sample was below the limit of detection for the Ag assay and that these results reflect test performance rather than characteristics of the study population.

# Assessment of the Overall Quality of the Evidence

## Research question 1 — Clinical effectiveness

No study met the inclusion criteria for Q1.

Table 22 of Appendix 10 reflects the lack of available data to make a Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment.

## Research question 2 – Frequency of harms

The single study on frequency of harms was a non-comparative study and did not provide an estimate of effect on HCV screening.

As such, Table 23 of Appendix 10 reflects the lack of available data to make a GRADE assessment.

## Research question 3 — Cost-effectiveness

The methods for the assessment of a body of evidence derived from cost-effectiveness analyses have not yet been established by the GRADE working group. Therefore, a GRADE evidence profile was not created.

## Research question 4 — Patients' preferences and values

A total of five main findings on participant preferences and values related to HCV screening were derived from the descriptive themes. The five review findings are, as follows:

1. Knowledge of and desire to know HCV status, level of perceived personal risk, and knowledge of HCV influence the decision to be screened.
2. People consider the implications for and availability of management for HCV when deliberating about screening.
3. Decisions about HCV screening are influenced by psychological and interpersonal contexts such as fear, embarrassment, denial, interest in personal health, concern for others, and relationships with others.
4. Preferences around implementation of screening include views about consent and initiators of testing, clinical setting of screening, test methods, and delivery of test information and results.
5. PWID and inmates experience unique barriers to HCV screening related to stigma and access to health care.

Each review finding began with a high level of confidence, which was reduced according to the severity of concerns about the evidence in any of the four CERQual domains: methodological limitations, relevance, adequacy of data, and coherence of evidence. The CERQual approach classifies confidence in review findings as high, moderate, low, or very low.

The level of confidence was graded as moderate for the three main findings pertaining to the first descriptive theme, regarding knowledge of HCV and HCV status, implications for the management of HCV, and the influence of interpersonal and psychological contexts on the decision to screen. The level of confidence in the findings was downgraded from high to moderate because of moderate concerns regarding methodological limitations (first review finding), relevance (second review finding), or both (third review finding). The first review finding was based on studies that demonstrated problematic sampling methods and were at risk of social desirability bias that could overestimate acceptance of screening. The second review finding was associated with moderate concerns related to population relevance; the studies contributing to this finding studied high-risk and general populations, but it is unclear whether individuals from high prevalence populations were well-represented. The third review finding presented the same concerns related to population relevance. It also suffered from the methodological limitations of two key studies[63,67] related to participant selection methods, potential for social desirability bias, and insufficient reporting on the interview process and analysis strategy.

The fourth and fifth main findings (preferences around implementation and populations with unique barriers to screening), which were related to the second descriptive theme, were judged to be findings with low confidence. The fourth review finding was downgraded from high to low confidence because of major concerns about adequacy and moderate concerns about methodology, relevance, and coherence of the data. The studies contributing to this review finding provided generally thin data, particularly regarding situations in which the various reported preferences about HCV screening would be important. The moderate methodology concerns for this finding were driven by major limitations in two studies[58,67] related to insufficient reporting of several aspects of study conduct. The setting of studies contributing to the fourth review finding (e.g., prisons and community-based resource centres) may reflect HCV screening implementation preferences that are not relevant to the primary health care setting of interest for this review. Inconsistency across these studies was also noted regarding which implementation factors were considered to be important. The level of confidence in the fifth review finding was judged to be low because of major methodological limitations and moderate concerns about relevance and adequacy of the data. Two studies[66,67] contributing to this finding presented major concerns related to participant selection, risk of social desirability bias, and the use of a researcher-defined questionnaire that did not allow for participants' expression in their own words. As this finding was specific to unique barriers to screening experienced by PWID and inmates, there was partial relevance to the entire population of interest for this review. Few studies were identified that contributed to this finding; however, as they provided relatively rich data, the adequacy concerns were judged to be moderate rather than major.

Table 24 of Appendix 10 summarizes the key findings from the descriptive evidence synthesis and gives the level of confidence in the evidence for each of these findings, as assessed using the CERQual approach.

## Research question 5 — Clinical validity

The evidence on the clinical validity of Ab and Ag testing started out graded as high based on study design — all studies were cross-sectional — which was then downgraded according to the severity of concerns about the evidence in any of the GRADE domains: risk of bias, indirectness, inconsistency, imprecision, and publication bias. The GRADE approach classifies confidence in review findings as high, moderate, low, or very low.

### Ab Tests

Twenty-three studies[70-84,86-89,91-94] evaluated the proportion of Ab test-positive patients who were confirmed to have active infection by PCR (Ab+RNA+/all Ab+), and the proportion of Ab test-positive patients who were confirmed to be free from active infection by PCR (Ab+RNA-/all Ab-). Based on individual study assessments using the QUADAS-2 tool,[53] there was an unclear risk of bias related to the patient selection, screening test, and diagnostic test domains for approximately one-third of studies because of the limited reporting of methods. This was considered to be a serious limitation that would affect the confidence in the results; therefore, the quality of evidence level was downgraded by one point to moderate.

Two studies[70,80] evaluated the proportion of Ab test-negative patients who were confirmed to have active infection by PCR (Ab-RNA+/all Ab-), and the proportion of Ab test-negative patients who were confirmed to be free from active infection by PCR (Ab-RNA-/all Ab-). The overall risk of bias was determined to be serious; the patient selection methods were unclear for one study,[80] which affected confidence in the range of results for these outcomes. Consequently, the quality of the evidence was downgraded by one level to moderate.

For all outcomes, indirectness was not considered to be serious, as the study population, screening tests, and diagnostic tests used in all studies were relevant to the review research questions and met the inclusion criteria.

Inconsistency was judged to be serious for all outcomes, as there was a wide range of reported values that could have been affected by inter-study variation in population, type of screening test, or combination of tests used, or specific PCR protocol followed, but it was unclear which factors influenced results the most. As a result of this uncertainty, the quality of evidence was again downgraded for all outcomes from moderate to low.

There was no evidence to assess imprecision, as no confidence intervals were reported, and there was no evidence of publication bias.

The final GRADE evidence quality level for all Ab test outcomes was low.

Details regarding GRADE assessments for studies evaluating Ab tests can be found in Table 25 in Appendix 10.

### Ag Tests

Four studies[24,80,85,90] evaluated the proportion of Ag test-positive patients who were confirmed to have active infection by PCR (Ag+RNA+/all Ag+), and the proportion of Ag test-positive patients who were confirmed to be free from active infection by PCR (Ag+RNA-/all Ag+). There was a high risk of bias regarding the screening test in one study[90] and an unclear risk of bias for patient selection in another study.[80] As there were possible quality issues in half the studies for this outcome, the risk of bias assessment presented serious limitations that reduced confidence in the study results, and the quality of the evidence was downgraded by one level to moderate.

One study[80] evaluated the proportion of Ag test-negative patients who were confirmed to have active infection by PCR (Ag-RNA+/all Ag-), and the proportion of Ag test-negative patients who were confirmed to be free from active infection by PCR (Ab-RNA-/all Ag-). Limited reporting regarding patient selection methods introduced an uncertain risk of bias. As this was the sole study providing data for this outcome, this limitation was judged to be serious and the quality of evidence was downgraded by one level to moderate.

For all outcomes, indirectness was not considered to be serious, as the study population, screening tests, and diagnostic tests used in all studies were relevant to the review research questions and met the inclusion criteria.

Inconsistency was judged to be serious for all outcomes. There was a wide range of reported values for the proportions of Ag test-positive patients with and without active viremia that could have been affected by inter-study variation in population, the number of Ag-positive individuals indentified in each study, the type of screening test used, or specific PCR protocol followed, but it was unclear which factors influenced results the most. Furthermore, a single study contributed data to the proportions of Ag test-negative patients with and without active viremia; therefore, heterogeneity could not be assessed and confidence in the results was reduced. As a result of this uncertainty, the quality of evidence was again downgraded for all outcomes from moderate to low.

There was no evidence to assess imprecision, as no confidence intervals were reported, and there was no evidence of publication bias.

The final GRADE evidence quality level for all Ag test outcomes was low.

Details regarding GRADE assessments for studies evaluating Ag tests can be found in Table 26 in Appendix 10.

# Discussion

Most of the evidence reported in this review comes from 12 studies on patient preferences and values on screening for HCV infection, and 26 studies on the clinical validity of screening for HCV infection with Ab or Ag tests in asymptomatic, non-pregnant adults. One study each was found on the frequency of harms and cost-effectiveness of HCV screening; therefore, results should be interpreted with caution. No published study on the comparative clinical effectiveness of HCV screening versus no screening met the inclusion criteria.

The summary of findings is followed by a commentary on the generalizability and limitations of the review.

## Summary of findings

### Clinical effectiveness

No evidence was identified regarding the clinical effectiveness of HCV screening compared with no screening. This is consistent with the findings of the 2013 USPSTF systematic review that did not identify any studies to address their research question regarding the impact of screening for HCV infection in non-pregnant adults without known abnormal liver enzyme levels on morbidity, mortality, quality of life, and HCV incidence.[38] No recommendations regarding HCV screening in this population were produced by the USPSTF; rather, the guideline based on this systematic review recommends targeted screening in high-risk populations and one-time screening in the birth cohort of 1945 to 1965.[99] Likewise, the CDC strongly recommends HCV screening in the same groups as the USPSTF, and does not recommend general population screening.[42] For people who are part of a high HCV seroprevalent population or who have a history of high-risk exposure or behaviour, the World Health Organization also makes a strong recommendation that testing for HCV Ab should be offered, although the 1945 to 1965 birth cohort is not specifically listed.[39] This recommendation was based on moderate-quality evidence.

The CDC reported that the HCV seroprevalence in the 1945 to 1965 birth cohort in the US is higher than that of the general population at 3.25%.[100] The USPSTF noted that the increased HCV prevalence in this birth cohort may be related to a much earlier history of high-risk behaviour or exposure to unscreened blood transfusions prior to 1992.[99] While targeted screening of high-risk individuals may be a more efficient screening strategy than a birth cohort-based screening strategy (fewer people need to be screened to identify one person with HCV infection in a risk-based screening strategy), the USPSTF concluded that 1945 to 1965 birth cohort screening would provide a similar benefit to risk-based screening because of the large number of Americans who belong to this birth cohort.[99] Similarly to the evidence-based guidelines produced in the US, a position statement from the Canadian Liver Foundation suggests that all adults born from 1945 to 1975 should undergo testing for hepatitis C.[101] This position statement referred to the USPSTF recommendations, which stated that HCV is most

prevalent in this subpopulation, and commented that risk-based testing has been unable to identify all individuals with HCV infection. However, a specific prevalence for this birth cohort in a Canadian population or direct evidence to support an expanded birth cohort compared with the American recommendations was not provided.

As the value of birth cohort screening is linked to HCV prevalence in those groups, the comparability of HCV prevalence in Canadian and American birth cohorts is a consideration for the applicability of the American screening guidelines to a Canadian clinical setting. In 2011, PHAC used back-calculation and workbook methods to estimate the prevalence of chronic HCV infection in Canada overall (0.64%), as well as in certain birth cohorts.[7] While the evaluated birth cohorts from 1950 to 1974 had a higher estimated HCV prevalence than the overall Canadian population (1950 to 1954, 1.25%; 1955 to 1959, 1.5%; 1960 to 1964, 1.2%; 1965 to 1969, 1.1%; 1970 to 1974, 0.8%), these estimates were consistently lower than the HCV prevalence in the American 1945 to 1965 birth cohort. Furthermore, PHAC estimated that the prevalence of chronic HCV infection in persons born before 1949 has decreased since 1991 to below the overall prevalence rate in Canada.[7] A Canadian study is currently underway assessing the seroprevalence in the 1945 to 1974 birth cohort to add to the body of evidence regarding HCV prevalence in Canada, which may inform deliberations about the importance of screening for chronic HCV infection in this group (Dr. Jordan Feld: personal communication, 2016 Dec).

While no studies directly assessing the clinical effectiveness of HCV screening in asymptomatic adults were identified for this review, it is anticipated that any benefit of screening would be closely linked to the availability of early treatment for those who would be detected by screening. Modelling studies based on European populations have shown that increasing both HCV diagnosis and treatment rates over time given the availability of newer DAA therapeutic options would reduce HCV prevalence, as well as HCV-related morbidity (e.g., cirrhosis, hepatocellular carcinoma) and mortality.[102-104] Based on the CADTH Therapeutic Review *Drugs for Chronic Hepatitis C Infection*,[29] the CADTH Canadian Drug Expert Committee recommends that all patients with chronic HCV infection, regardless of fibrosis score, should be considered for treatment; however, the CADTH Canadian Drug Expert Committee also notes that it may not be feasible to treat all patients with the available resources of the health care system, so treatment of patients with severe disease should be prioritized.[105] Therefore, the potential benefits of an HCV screening program may be minimized if asymptomatic individuals with HCV infection identified by a screening program do not receive treatment until they have more severe disease. However, additional benefits to the recognition of asymptomatic HCV infection include counselling regarding other forms of liver injury such as alcohol and fatty liver disease, as well as the prevention of transmission of infection to others. As the costs of treatment decrease, treatment access may also expand.

## Frequency of harms

One non-comparative, observational study met the inclusion criteria for the question on frequency of harms.[4] Among 681 anti–HCV-positive patients seen at a Veterans Affairs Medical Center in the US, 670 were tested for HCV-RNA and 520 were confirmed positive (confirmation of viremia was missed in 11 patients). One patient was hospitalized for one night of pain control following a liver biopsy. This outcome from a liver biopsy may not be particularly relevant to HCV screening, as it may be considered a treatment prioritization step and is performed much less frequently for fibrosis staging since the introduction of effective non-invasive tools like transient elastography, which has replaced liver biopsy in some centres in Canada.[40] Other than missing confirmatory test results from fewer than 2% of samples (11 out of 681), bias due to deviations from the protocol was not evident. Potential bias due to measurement of outcomes could not be assessed, as the process with which harms were measured was not adequately described. Likewise, bias in selection of reported results could not be assessed.

## Cost-effectiveness

The authors of the included cost-effectiveness analysis considered the impact of one-time "screen-and-treat" strategies for patients with chronic HCV monoinfection.[35] The authors incorporated three treatment scenarios: Tx1, Tx2, and Tx3. In scenario Tx1, all patients (infected with HCV genotypes 1 through 6) received PR. In scenario Tx2, patients with genotype 1 infection received simeprevir plus PR, and patients with genotypes 2 and 3 received sofosbuvir plus ribavirin. In scenario Tx3, patients with genotype 1 infection received interferon-free combination therapy, and patients with genotypes 2 and 3 received sofosbuvir plus ribavirin. Patients with genotypes 4, 5, and 6 received PR in all scenarios.

For individuals 25- to 64-years-old and living in Canada, a screen-and-treat intervention resulted in ICERs ranging from $34,783/QALY to $42,398/QALY compared with no screening. The most cost-effective option was Tx3 in this age group. For individuals 45- to 64-years-old, screen-and-treat resulted in ICERs ranging from $34,359/QALY to $44,034/QALY. The most cost-effective option was Tx1 in this age group. Therefore, a one-time screen-and-treat strategy was found to be cost-effective at a willingness-to-pay threshold of $50,000/QALY for both evaluated birth cohorts, one representing a large proportion of the Canadian adult general population (age 25 to 64) and the other representing a high-prevalence subgroup of the general population (age 45 to 64). One-way sensitivity analysis suggests the model was robust to screening acceptance rates and cost of screening. When compared with no screening only, probabilistic sensitivity analyses demonstrated that the chances that screening and treatment would cost less than $50,000/QALY were 56% for Tx1, 51% for Tx2, and 60% for Tx3.

The HCV management landscape is rapidly evolving with the development of rapid tests and markedly improved treatment options. The accompanying changes to available treatment options for HCV infection will have important implications for cost-effectiveness of screening and subsequent treatment.

This cost-effectiveness analysis may no longer be relevant as newer, more effective, simpler options become available and the costs of treatment change; however, it is expected that screen-and-treat strategies will become more cost-effective, especially if costs of treatment decrease.

## People's preferences and values regarding HCV screening

Twelve studies[58-69] provided evidence related to participants' preferences and values regarding the decision to be screened for HCV. The results of these studies revealed that people make decisions about screening while considering their immediate context and the perceived consequences and implications of a positive test result, including the availability and effectiveness of HCV treatment and concerns about passing on an HCV infection. Furthermore, an individual will make a screening decision that appears reasonable to them, based on their own life situation, psychological context, and unique knowledge about screening and HCV in general. Of note, participants did not include considerations of specific HCV-related clinical outcomes (e.g., liver cancer, liver transplant, cirrhosis) in their discussions of screening decisions. This may reflect a generally limited knowledge of HCV-related disease progression, or that concern about specific clinical events is not the primary driver of this decision.

People also hold preferences regarding the implementation of their decision to screen. They generally expressed a desire for confidential and convenient testing in a comfortable environment, and preferred screening situations in which they could appropriately receive sufficient information about HCV and the test, and obtain results quickly. Some issues differed among subsets of the general population, such as concerns about stigma and access to health care among PWID and inmates, which may require special consideration for the implementation of screening programs involving these groups.

## Clinical validity

A total of 26 studies[24,70-94] were included for the research question on the clinical validity of screening with Ab or Ag tests. Study populations consisted of asymptomatic individuals selected from the general population, blood banks, and clinic or hospital settings across several countries, screened with a variety of Ab and Ag tests, including ELISAs, CMIAs, ECLIAs, and MEIAs.

There was a wide range in the proportion of HCV Ab-positive or Ag-positive patients with chronic HCV infection reported across studies, from 0% to 89.7% with the Ab tests and 0% to 100% with the Ag tests. Specifically, these results were fairly consistent when focusing on the tests commonly used in Canada. Laboratory directors have reported that the Abbott ARCHITECT anti-HCV CMIA and the ARCHITECT HCV Ag CMIA are used for hepatitis C screening in some Canadian public health laboratories (Dr. Jordan Feld: personal communication, 2016 Dec). Included studies that evaluated the ARCHITECT anti-HCV test showed that the proportion of Ab-positive patients who also tested positive for HCV-RNA ranged overall from 10.1% to 80.3%. One study that evaluated the ARCHITECT HCV Ag CMIA reported that 100% of Ag-positive samples (n = 154) were also RNA-positive.[80] These ranges of results do not necessarily reflect test

performance alone but may also have been influenced by other factors, including variability in study populations and the number of Ab-positive or Ag-positive samples identified. Furthermore, some studies evaluated tests that are not commercially available or commonly used in Canada, which limits the relevance of these study findings to current clinical practice in a Canadian setting.

The focus of this review on the clinical validity of HCV Ab and Ag screening tests is distinct from the analytical validity of Ab and Ag tests, which has been established. Third-generation EIAs have a reported sensitivity of 97.5% to 100%, and a reported specificity of over 99% to detect HCV Abs in blood donor and clinical samples.[106] The limit of detection of a currently available HCV Ag test is 3.00 fmol/L,[80] and, while less sensitive than HCV-RNA assays, Ag tests have demonstrated a sensitivity of over 90% and specificity exceeding 98%.[23,107] The clinical validity of a screening test is determined by the ability of that test to act as a good surrogate for a diagnostic test, such as PCR to detect viral RNA; therefore, a high proportion of Ab-positive or Ag-positive patients who are also RNA-positive by PCR would generally indicate good clinical validity of the Ab or Ag tests. The inconsistency of observed results among Ab test studies and Ag test studies may reflect differences in performance between the various tests evaluated, but it may also be affected by the underlying HCV prevalence in the source populations, the number of individuals included in the study, or other sources of population variation between studies. For example, the proportion of Ab+RNA+ individuals among all Ab+ samples identified with Ortho HCV version 3.0 ELISA in a general population (five studies[86,88,89,91,93]) ranged from 46.7% to 87.5%, and the studies contributing to the upper and lower ends of that range were conducted in Italy — a country with a reported point seroprevalence of 2.0% but that ranges from 1.6% to 7.3%.[45]

Another five studies[24,79,83,90,92] reported that none of the Ab+ or Ag+ individuals were found to be RNA+ by PCR, which may also be a finding that is influenced by prevalence. As studies were eligible for inclusion in this review if they were conducted in a country with an average HCV seroprevalence of less than 3.5%, it is possible that the sample sizes in some of these studies ($n < 600$ in three studies[24,79,92]) were not large enough to adequately represent the proportion of individuals in the total population with chronic HCV infection. For this reason, and all other factors being equal, results from studies with larger sample sizes may be more reliable. However, two[83,90] of the five studies had large sample sizes ($n = 1{,}004$[90] and 1,007[83]), suggesting that overall study sample size is not the only contributing factor to the observed results. As the outcomes of interest for this review included the proportions of Ab-positive or Ag-positive samples that were also RNA-positive, a sufficient number of samples would have to be identified with the screening test to understand how well this corresponds with a result on the PCR test. For example, when one sample is screening-test positive, the only possible proportions of samples also testing positive on the PCR test are 0% and 100%, which likely does not accurately reflect what the results would be if more samples were tested with PCR. Six studies reported that fewer than 20 screened samples tested positive for

Ab.[71,72,78,79,83,84] In addition, two of the four included Ag test studies reported that two samples or fewer tested positive for Ag.[24,90]

It is not necessarily unexpected that the upper range of Ab+RNA+ results was lower than that of Ag+RNA+ results, as the presence of Ag reflects current infection and the presence of HCV Abs reflects exposure to HCV. Given that 15% to 50% of people infected with HCV spontaneously clear the virus,[9,16] up to one-half of all Ab-positive individuals could be RNA-negative by PCR. Based on results reported by studies with a large sample size (n > 1,000) in a general population (i.e., in contrast to blood donors who are likely pre-screened), Ab tests appear to be moderately good at identifying individuals with active HCV infection, as the proportion of Ab-positive individuals with HCV viremia ranged from 71.0% to 87.5% in these five studies.[75,86,88,89,93] In a screening scenario, this would mean that up to 29% of Ab-positive people would unnecessarily proceed to RNA testing. This may be acceptable for the first step in a screening pathway, since the main goal is to avoid missing cases (screening-in is more important than screening-out), and there are few harms associated with a non-invasive diagnostic test like PCR.

Data on the proportion of Ab-negative individuals with active viremia (Ab– RNA+ of all Ab– samples) were available from two studies and reported as 0.3% (two of 796 ED patients)[70] and 26% (five of 19 patients from a hospital microbiology department).[80] While limited evidence was identified to address this issue, a minority of Ab-negative individuals may be incorrectly assumed to be HCV infection-free and theoretically would not proceed for subsequent diagnosis and treatment, if necessary. However, variability in the study populations and the total number of negative samples identified may have impacted the results; therefore, these findings should be interpreted with caution.

A recent systematic review was published on the diagnostic test accuracy of Ab and Ag tests for HCV infection screening in asymptomatic adults, and the results followed a similar trend to this report.[108] This review reported a wide range of positive predictive values for HCV Ab screening tests relative to an RNA-based reference standard test (13.8% to 90.0%). The systematic review identified one study that compared a dual Ab/Ag test with an RNA-based reference standard, and reported a positive predictive value of 44.6% for this test.[108] It is possible that the range of results reported in this systematic review was also influenced by variability between studies in the patient populations.

Overall, the heterogeneity between study interventions and source populations across the 26 studies included in this review introduced uncertainty and reduced the quality of evidence contributing to each outcome for this review question. The limited quality of the evidence identified for this report precludes clear conclusions about the clinical validity of a particular Ab or Ag test or screening pathway.

### Targeted screening of high-risk and high prevalence populations

Among the studies that were included for the research questions on harms, cost-effectiveness, and people's views of HCV screening, there was little evidence to address the impact of targeted screening of high-risk and high HCV prevalence populations. The study on frequency of harms included patients who may have had a history of mental illness,[4] and the cost-effectiveness analysis focused on birth cohort screening (adults aged 25 to 64 years, and 45 to 64 years).[35] Studies on people's preferences and values included a high prevalence birth cohort (the "baby boomer" generation in the US born from 1945 to 1965),[58-60] and people who were at high risk for HCV due to IDU,[60-63,66] incarceration,[67,69] or other known risk factors.[65] In one study, the acceptability of screening in a high-risk urban population did not change after an educational intervention that significantly improved knowledge of HCV, as acceptance of screening was already high at baseline.[63] The majority of participants in this population stated that they would want treatment if they tested positive for HCV (98%), that every HCV-positive individual should be treated (76%), and that other HCV-positive members of their community would seek treatment (76%). This study also found that even in the absence of available treatment, the offer of healthy lifestyle advice for people who tested positive for HCV increased participant willingness to undergo screening from 90% to 96%.

High-risk and high-prevalence populations were out of scope for the question on clinical validity of HCV screening with Ab or Ag tests. There may be benefits and/or a difference in clinical effectiveness of screening with these tests in these populations that were not addressed in this review.

Developments in treatment options and the accompanying changes to treatment algorithms, clinical effectiveness, costs, and funding policies will have important implications for HCV screening.

## Generalizability of findings and relevance to the Canadian clinical context

Generalizabilty refers to the representativeness (or relevance) of the available evidence to the population of interest. This population consists of asymptomatic, non-pregnant, treatment-naive residents of Canada, and for Q1 to Q4 includes the specific evaluation of marginalized groups, such as PWID, incarcerated individuals, and immigrants; therefore, the results of this review may not be entirely generalizable to the screening of certain groups that did not meet selection criteria according to the focus of this review, such as pregnant women, health care workers, and people with HIV. The ranking of relevant clinical effectiveness and harms outcomes of screening selected to be assessed within this review was performed by the CTFPHC HCV working group. To contribute to considerations for outcome ranking, the CTFPHC's HCV working group recruited to 19 individuals, with and without HCV infection, who were intended to be representative of the Canadian general population.[41] Details about participant demographics were not available, so it is unclear how representative this group of patients may have

been, or whether the opinions of high-risk individuals or members of high-prevalence groups were solicited or considered.

A strength of this review is that some of the evidence gathered came from subgroups at high risk of HCV infection; however, this evidence may not be generalizable to other subgroups of the general population. For example, the study on frequency of harms was limited to participants at a Veterans Medical Center, where the level of care may differ from that offered to the general population, or that accessed by marginalized groups.[4] People who regularly access care are expected to have different outcomes compared with those who do not. The impact of screening on clinical harms of marginalized subgroups of the population — such as PWID, incarcerated individuals, and immigrants — merits further investigation. Information on stigma likewise came primarily from PWID, and their perspectives may not be representative of other groups.[61,66,67]

There are some considerations regarding generalizability of the evidence from the cost-effectiveness study.[35] First, the base case of the cost-effectiveness study evaluated the screening and treatment of chronic HCV infection for a birth cohort from the general Canadian population (ages 25 to 64). While this age range captures a large segment of the adult population, the authors of this economic evaluation note that the findings may not be generalizable to subgroups of the population who may have a higher risk of HCV infection; however, it is anticipated that targeted testing of high-risk individuals would be more cost-effective than general population screening. Second, the study assumed that all individuals who tested positive for HCV antibody would proceed to an HCV-RNA confirmatory test. This would be a valid assumption if reflex RNA virus testing was done on all Ab-positive samples. On the other hand, it may have overestimated the clinical effectiveness of screening in a general population and may not apply to populations in which only a subset of anti-HCV-positive individuals return for this confirmatory test. This particular parameter was indirectly included in sensitivity analyses; adjustments to the acceptance of screening value or the probability of receiving treatment in sensitivity analyses did not greatly impact the ICERs. The specific treatment regimens evaluated in this study remain relevant to current clinical practice in Canada; however, their relevance may change as new, more effective, and potentially less costly treatments become available.

Three studies that explored participant preferences and values used a qualitative descriptive design, and five of the ten studies that implemented a survey focused on participants who were at high risk for HCV, predominantly due to IDU or incarceration in a correctional facility.[60-63,65-67,69] While these are relevant groups to target for HCV screening, as recommended in the USPSTF guidelines,[99] it is uncertain whether the views and preferences held by individuals in these specific high-risk groups would be transferrable to a larger, more general population including low-risk individuals. The USPSTF and CDC guidelines also recommend one-time HCV screening for individuals born between 1945 and 1965;[42,99] while some studies identified for this review included members from this high-prevalence birth cohort,[58-60] the data were not sufficiently rich to suggest that the perspectives of this group are adequately represented in this review. In addition, studies that

specifically evaluated the views and preferences of other marginalized populations, such as migrants and the elderly or socially isolated, were not identified for inclusion in this review. For example, while evidence on stigma focused on PWID, this issue may also be relevant to other high-risk populations and also potentially low-risk populations. As with cost-effectiveness, this review captures perspectives and views over a short period of time. Many studies were conducted during a time when peginterferon and ribavirin were the main or only treatment regimen available. The perspectives and views presented in these studies may not remain relevant in the future, considering potential changes in the demographics and evolving treatment options. For example, given the higher cure rates and more tolerable side effect profile of the new interferon-free DAA regimens, it is possible that attitudes toward screening would become more favourable as these treatment options become more available.

Overall, the 26 studies that reported outcomes related to clinical validity of screening with Ab and Ag tests suffered from methodological issues that limited confidence in the results and their representativeness of how the screening tests would perform in a clinical scenario of general population screening. Specifically, it was unclear whether the choice of Ab and Ag screening tests and pathways (including supplemental or secondary tests), and diagnostic PCR tests used in the studies, were reflective of those commonly used in Canadian clinical practice (for example, the Ortho HCV Core Antigen ELISA, evaluated in two included studies,[24,85] was not identified in the Health Canada Medical Devices Active License Listing). Furthermore, some Ab tests used in Canadian public health laboratories, such as the Siemens ADVIA Centaur HCV assay (Dr. Jordan Feld: personal communication, 2016 Dec), were not represented in any of the included studies in this report. It was also unclear whether all of the study populations were adequately representative of a Canadian general population. One issue is related to the prevalence of HCV in different countries. The overall prevalence of chronic HCV infection in Canada is relatively low, and has been estimated at 0.64%[7] to 0.8%.[45] No Canadian studies regarding the clinical validity of general population screening with Ab and Ag tests were identified. However, studies conducted in low-to-moderate HCV seroprevalence countries (HCV seroprevalence point estimate of 3.5% or less[44,45]) were eligible for inclusion to ensure a thorough review, allowing for the inclusion of a variety of countries with variable reported HCV seroprevalence values that are higher than the prevalence of HCV in Canada. Furthermore, there may be intra-country variability in HCV prevalence (e.g., Italy), which increases the uncertainty for studies conducted in those countries regarding how closely that particular study population mirrors what would be expected in Canada. It is also uncertain whether screening studies that use samples from blood banks are truly representative of or applicable to a general population, given that donated blood is typically collected from blood donors who have already undergone pre-screening with some sort of health assessment questionnaire to eliminate persons suspected of having or being at risk for infectious diseases, including HCV infection. One Ag test study[90] focused on

seroconversion in blood donors, which more closely reflects the diagnosis of acute HCV rather than a screening scenario for chronic HCV infection.

## Study limitations

This review was limited by the lack of evidence identified for the research questions on the comparative clinical effectiveness of HCV screening versus no screening. The main review outcomes were long-term clinical outcomes (e.g., hepatocellular carcinoma, mortality), as these are ultimately the most important measures of success for an HCV screening program; however, conducting long-term studies is resource intensive and generally more difficult than for short-term studies, which may partially explain the absence of published clinical trials that specifically address these outcomes. This does not necessarily mean that HCV screening is ineffective, particularly given the results from modelling studies demonstrating that increased HCV diagnosis and treatment rates would decrease HCV-related morbidity and mortality.[102-104] Rather, it suggests that strong conclusions cannot be provided here because of the paucity of evidence identified for this review.

The population of interest was designed to reflect a general population (irrespective of risk factors) eligible for a universal HCV screening program; however, the perspectives and experiences of members of certain subgroups that were beyond the scope of this review — such as pregnant women, health care workers, and people with HIV — may be relevant. For example, PWID are at high risk for both HCV and HIV, and up to 80% of PWID with HIV are also co-infected with HCV.[109] For this reason, many screening guidelines suggest concurrent screening for HCV and other infections, which suggests that it would be relevant and valuable to consider the perspectives regarding screening held by individuals in this group. In addition, the setting of interest for this review was limited to primary care or other settings in which HCV screening is likely to occur. Therefore, individuals in marginalized groups who may not access primary health care services were likely underrepresented.

Subgroup analyses for risk-based versus prevalence-based screening was planned but ultimately not done because of a lack of included studies. As previously mentioned, it is possible that there are differences in screening outcomes between different subpopulations, including certain birth cohorts, immigrants, and individuals at high risk due to IDU or incarceration.

Specific to the frequency of harms, the results cannot be used to make conclusions about the harms of not screening; although it is expected that, in the absence of screening, more patients will be diagnosed at later stages of HCV infection. Designing studies that will provide evidence to assess the harms of not screening could be ethically problematic and may require a large study population and an extremely long follow-up period given the relatively slow progression of liver damage and its ensuing complications.

The evidence review regarding the clinical validity of screening with Ab and Ag tests was limited by the number of studies that did not pursue PCR testing in patients who tested negative on the initial screening tests. These study designs reflected a clinical screening scenario in which only screening

test-positive patients would continue through the diagnostic pathway and screening test-negative patients are assumed to be free of chronic HCV infection. However, direct evidence confirming the appropriateness of this assumption for each screening test by testing Ab-negative and Ag-negative patients for HCV-RNA would support a conclusion of its clinical validity for screening a general population, which is expected to contain relatively few individuals with undiagnosed, chronic HCV infection. Furthermore, becasuse of the pre-seroconversion window period of up to 12 weeks,[17] it is possible that some individuals in the early stages of HCV infection would not be identified by Ab testing, and therefore RNA testing may be valuable to identify these individuals despite an initial negative result on the screening test. However, this may not be a priority in a general population screening program, as the number of HCV-infected individuals in the window period in a low-prevalence country that would be detected by one-time screening would likely be extremely low, and it may not be feasible to test all Ab-negative individuals in order to identify them.

Strong conclusions about the clinical validity of the evaluated screening tests are also limited by the heterogeneity among studies with respect to the populations and settings, choice of tests, and definition of test positivity; this heterogeneity may have contributed to the wide range of observed results for each clinical validity outcome. In addition, the included studies tested all Ab-positive samples for HCV-RNA, simulating reflex RNA testing in clinical practice. However, recall testing for individuals who test positive for HCV Ab is another common screening strategy, and some of these individuals may not follow up for subsequent RNA testing. Reflex RNA testing could potentially be performed on all anti-HCV Ab-positive tests identified from general population screening, but the costs and practicality of this approach would have to be evaluated in specific clinical settings. Using RNA as the initial testing strategy is not practical because of cost considerations, as well as the risk of false-positive tests due to cross-contamination, which is always a concern in studies using high-volume PCR approaches.[25]

## Directions for future research

Most of the information included in this review involves participants from outside Canada. Evidence is needed from screening scenarios relevant to populations living within Canada to augment the limited data that is currently available. In the absence of screening data, retrospective evaluations of HCV-infected patients or appropriate modelling studies could provide useful projections about the potential impact of screening for chronic HCV infection. Other than determining prevalence, the primary purpose of screening is to identify individuals who may benefit from available treatment options and who may also make lifestyle choices to prevent transmission of their infection, as well as to slow progression of liver damage. To generate the evidence required to assess the impact of screening, long-term studies will be needed that compare the treatment outcomes of individuals who are screened with those who are not. Studies would also need to include a variety of individuals with diverse risk levels and HCV history. Developing such a study with sufficient power to evaluate the impact of screening would require a significant amount of time and resources. Given the well-documented burden of HCV in

Canada, the aging of the infected population, and the high efficacy and safety of new therapies, it is questionable whether a study of randomizing populations to screening or no screening would be ethical.

A health technology assessment recently released by the University of Calgary[40] evaluated the cost-effectiveness of birth cohort screening in Alberta; this evaluation used the same model presented by Wong et al.[35] and adjusted some model parameters to reflect age distribution, HCV prevalence, screening uptake, and treatment costs in Alberta. This study showed that all evaluated combination screening and treatment strategies were cost-effective at a willingness-to-pay threshold of $50,000 per QALY. However, as this model was derived from the model by Wong et al., it is subject to the same limitations as the original model described in this review and does not provide any additional information about populations not addressed by Wong et al., such as high-risk groups. Therefore, additional economic evaluations regarding the cost-effectiveness of general population screening for HCV in a Canadian primary care setting are required. More studies are also required to examine the cost-effectiveness of targeted HCV screening for high-risk groups in Canada, although if general population screening is consistently shown to be cost-effective, it is expected that targeted screening of high-risk groups would likely be cost-effective, as well. It would be useful to compare the cost-effectiveness of age-based screening approaches to the risk-based strategy currently advocated by PHAC.[110]

Based on an assessment using the CERQual approach, the level of confidence in the evidence regarding the preferences related to implementation of a decision to be screened for HCV was determined to be low; this was because of the narrow scope of the eight included studies that contributed data to this review finding.[58,59,61,62,64-67] It is unlikely that the list of implementation considerations in this review is exhaustive, and it is unclear in which situations each identified preference would be important. The potential for selection and social desirability biases identified in the studies involving PWID and inmates suggests that further research is needed to explore whether new barriers unique to these populations, or different views on the identified barriers, exist. Finally, the setting of interest for the current review, and therefore that of the included studies, is primary care and other settings generalizable to primary care in which HCV screening is commonly performed, such as community-based clinics and hospital EDs. This means that the findings in this review were mainly derived from studies of people who actively seek and access health care and other community resources, thereby potentially missing information on people who are not contacting the health care system. Future reviews with a broader scope for the setting of interest may capture different views and preferences about HCV screening from those individuals who do not regularly access primary care.

More evidence on the clinical validity of general population screening with Ab and Ag tests is needed in order to form clear conclusions regarding preferred tests or testing pathways. Ideally, studies would be conducted in Canada using screening and diagnostic tests commonly used in clinical practice to screen true general population individuals identified from the community or a primary care setting rather than a more selective population of blood donors.

## Conclusions

There is a paucity of clinical trial data regarding the clinical effectiveness and harms of screening compared with no screening; however, that does not necessarily suggest that screening would not be effective in clinical practice. The potential benefits of screening would be closely associated with the underlying prevalence of chronic HCV infection in the screened population and the availability of early treatment for asymptomatic individuals with HCV infection identified by a screening program. With respect to patient preferences and experiences, policy-makers should be aware that individuals make decisions about screening that appear reasonable and feasible within their own life situation, psychological context, and unique knowledge about screening and HCV in general. Individuals also hold preferences and face barriers regarding the implementation of the decision to screen. Some experiences and views about HCV screening were specific to certain high-risk groups, such as PWID and inmates, which may present important considerations for the implementation of screening programs for these groups. A large range was observed for the proportion of patients who tested positive on both an Ab or Ag test and a PCR test. Based on results reported by studies conducted in a general population with a large sample size (n >1,000), Ab tests may be acceptable as a first step in a screening pathway. These tests are able to identify individuals with active HCV infection, as the proportion of Ab-positive individuals with HCV viremia ranged from 71.0% to 87.5% in these studies. The uncertainty introduced by the heterogeneity between study interventions and source populations, as well as the low quality of evidence contributing to each outcome for this review question, precludes clear conclusions about the clinical validity of a particular Ab or Ag test in a screening pathway.

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# Appendix 1: Literature Search Strategy

| OVERVIEW: LITERATURE SEARCH STRATEGY FOR RESEARCH QUESTIONS 1 TO 4 | |
|---|---|
| Interface: | Ovid |
| Databases: | Ovid MEDLINE In-Process & Other Non-Indexed Citations<br>Embase 1974 to 2015 November 12 |
| Date of Search: | November 13, 2015 |
| Alerts: | Bi-weekly search alerts was run |
| Study Types: | Study design filters per unique question, as per protocol. See below strategy for exact applications |
| Limits: | Publication years 2000 to 2015<br>English and French language |
| **SYNTAX GUIDE** | |
| MeSH | Medical Subject Heading |
| Exp | Explode a subject heading |
| * | Before a word, indicates that the marked subject heading is a primary topic;<br>or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings |
| # | Truncation symbol for one character |
| ADJ | Requires words are adjacent to each other (in any order) |
| ADJ# | Adjacency within # number of words (in any order) |
| .ti | Title |
| .ab | Abstract |
| .pt<br>.kf | Publication type<br>Author-provided keyword |

| MULTI-DATABASE STRATEGY: RESEARCH QUESTIONS 1 TO 4 | |
|---|---|
| **Research Question 1 (Clinical Effectiveness):** | |
| 1 | Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/ or Hepatitis C Antibodies/ or exp Hepatitis C Antigens/ |
| 2 | (hepatitis C or hepC or hep C or hepacivirus* or HCV).ti,ab,kf. |
| 3 | 1 or 2 |
| 4 | exp Mass screening/ |
| 5 | (detect or detection or screen or screens or screened or screening).ti,ab,kf. |
| 6 | 4 or 5 |
| 7 | 3 and 6 |
| 8 | meta-analysis.pt. |
| 9 | meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ |
| 10 | ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab. |
| 11 | ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab. |
| 12 | ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab. |

| MULTI-DATABASE STRATEGY: RESEARCH QUESTIONS 1 TO 4 | |
|---|---|
| 13 | (data synthes* or data extraction* or data abstraction*).ti,ab. |
| 14 | (handsearch* or hand search*).ti,ab. |
| 15 | (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab. |
| 16 | (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab. |
| 17 | (meta regression* or metaregression*).ti,ab. |
| 18 | (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw. |
| 19 | (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw. |
| 20 | (cochrane or (health adj2 technology assessment) or evidence report).jw. |
| 21 | (meta-analysis or systematic review).md. |
| 22 | (comparative adj3 (efficacy or effectiveness)).ti,ab. |
| 23 | (outcomes research or relative effectiveness).ti,ab. |
| 24 | ((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab. |
| 25 | or/8-24 |
| 26 | (Randomized Controlled Trial or Controlled Clinical Trial).pt. |
| 27 | (Clinical Trial or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt. |
| 28 | Multicenter Study.pt. |
| 29 | Randomized Controlled Trial/ |
| 30 | Randomized Controlled Trials as Topic/ |
| 31 | "Randomized Controlled Trial (topic)"/ |
| 32 | Controlled Clinical Trial/ |
| 33 | Controlled Clinical Trials as Topic/ |
| 34 | "Controlled Clinical Trial (topic)"/ |
| 35 | Clinical Trial/ or Phase 2 Clinical Trial/ or Phase 3 Clinical Trial/ or Phase 4 Clinical Trial/ |
| 36 | Clinical Trials as Topic/ or Clinical Trials, Phase II as Topic/ or Clinical Trials, Phase III as Topic/ or Clinical Trials, Phase IV as Topic/ |
| 37 | "Clinical Trial (topic)"/ or "Phase 2 Clinical Trial (topic)"/ or "Phase 3 Clinical Trial (topic)"/ or "Phase 4 Clinical Trial (topic)"/ |
| 38 | Multicenter Study/ or Multicenter Study as Topic/ or "Multicenter Study (topic)"/ |
| 39 | Randomization/ |
| 40 | Random Allocation/ |
| 41 | Double-Blind Method/ |
| 42 | Double Blind Procedure/ |
| 43 | Double-Blind Studies/ |
| 44 | Single-Blind Method/ |
| 45 | Single Blind Procedure/ |
| 46 | Single-Blind Studies/ |
| 47 | Placebos/ |
| 48 | Placebo/ |
| 49 | Control Groups/ |
| 50 | Control Group/ |
| 51 | Cross-Over Studies/ or Crossover Procedure/ |

| MULTI-DATABASE STRATEGY: RESEARCH QUESTIONS 1 TO 4 | |
|---|---|
| 52 | (random* or sham or placebo*).ti,ab,hw. |
| 53 | ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw. |
| 54 | ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw. |
| 55 | (control* adj3 (study or studies or trial*)).ti,ab,hw. |
| 56 | (clinical adj3 (study or studies or trial*)).ti,ab,hw. |
| 57 | (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw. |
| 58 | (phase adj3 (study or studies or trial*)).ti,ab,hw. |
| 59 | ((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw. |
| 60 | ((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw. |
| 61 | allocated.ti,ab,hw. |
| 62 | ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw. |
| 63 | trial.ti. |
| 64 | or/26-63 |
| 65 | exp animals/ |
| 66 | exp animal experimentation/ |
| 67 | exp models animal/ |
| 68 | exp animal experiment/ |
| 69 | nonhuman/ |
| 70 | exp vertebrate/ |
| 71 | animal.po. |
| 72 | or/65-71 |
| 73 | exp humans/ |
| 74 | exp human experiment/ |
| 75 | human.po. |
| 76 | or/73-75 |
| 77 | 72 not 76 |
| 78 | 64 not 77 |
| 79 | epidemiologic methods.sh. |
| 80 | epidemiologic studies.sh. |
| 81 | cohort studies/ |
| 82 | cohort analysis/ |
| 83 | longitudinal studies/ |
| 84 | longitudinal study/ |
| 85 | prospective studies/ |
| 86 | prospective study/ |
| 87 | follow-up studies/ |
| 88 | follow up/ |
| 89 | followup studies/ |
| 90 | retrospective studies/ |
| 91 | retrospective study/ |
| 92 | case-control studies/ |
| 93 | exp case control study/ |

| MULTI-DATABASE STRATEGY: RESEARCH QUESTIONS 1 TO 4 | |
|---|---|
| 94 | cross-sectional study/ |
| 95 | observational study/ |
| 96 | quasi experimental methods/ |
| 97 | quasi experimental study/ |
| 98 | validation studies.pt. |
| 99 | (observational adj3 (study or studies or design or analysis or analyses)).ti,ab. |
| 100 | cohort*.ti,ab. |
| 101 | (prospective adj7 (study or studies or design or analysis or analyses or cohort)).ti,ab. |
| 102 | ((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab. |
| 103 | ((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data or cohort)).ti,ab. |
| 104 | (retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).ti,ab. |
| 105 | ((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab. |
| 106 | (case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab. |
| 107 | (population adj3 (study or studies or analysis or analyses)).ti,ab. |
| 108 | (descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab. |
| 109 | ((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab. |
| 110 | (cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab. |
| 111 | ((natural adj experiment) or (natural adj experiments)).ti,ab. |
| 112 | (quasi adj (experiment or experiments or experimental)).ti,ab. |
| 113 | ((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab. |
| 114 | (prevalence adj3 (study or studies or analysis or analyses)).ti,ab. |
| 115 | case series.ti,ab. |
| 116 | case reports.pt. |
| 117 | case report/ |
| 118 | case study/ |
| 119 | (case adj3 (report or reports or study or studies or histories)).ti,ab. |
| 120 | organizational case studies.sh. |
| 121 | or/79-120 |
| 122 | (disease adj2 (progress* or predict* or prognosis) adj2 (Outcome* or Risk* or Model*)).ti,ab,kf. |
| 123 | (Predict* adj2 (Outcome* or Risk* or Model*)).ti,ab,kf. |
| 124 | ((History or Variable* or Criteria or Scor* or Characteristic* or Finding* or Factor*) adj2 (Predict* or Model* or Decision* or Identif* or Prognos*)).ti,ab,kf. |
| 125 | ((Prognostic or prognostic) adj2 (History or Variable* or Criteria or Scor* or Characteristic* or Finding* or Factor* or Model*)).ti,ab,kf. |
| 126 | Disease model*.ti,ab,kf. |
| 127 | Decision*.ti,ab,kf. and *Logistic Models/ |
| 128 | 122 or 123 or 124 or 125 or 126 or 127 |
| 129 | 7 and 25 |
| 130 | 7 and 78 |
| 131 | 7 and 121 |

| MULTI-DATABASE STRATEGY: RESEARCH QUESTIONS 1 TO 4 | |
|---|---|
| 132 | 7 and 128 |
| 133 | 129 or 130 or 131 or 132 |
| 134 | limit 133 to english language |
| 135 | limit 133 to french |
| 136 | 134 or 135 |
| 137 | limit 136 to yr="2000 -Current" |
| 138 | 137 use pmez |
| 139 | exp hepatitis C/ or exp Hepatitis C virus/ or exp hepatitis C antibody/ or exp hepatitis C antigen/ |
| 140 | 2 or 139 |
| 141 | exp antibody screening/ or exp mass screening/ or exp screening/ or exp screening test/ |
| 142 | 5 or 141 |
| 143 | 140 and 142 |
| 144 | 25 and 143 |
| 145 | 78 and 143 |
| 146 | 121 and 143 |
| 147 | 128 and 143 |
| 148 | 144 use oemezd |
| 149 | 145 use oemezd |
| 150 | 146 use oemezd |
| 151 | 147 use oemezd |
| 152 | 148 or 149 or 150 or 151 |
| 153 | 152 not conference abstract.pt. |
| 154 | limit 153 to english language |
| 155 | limit 153 to french |
| 156 | 154 or 155 |
| 157 | limit 156 to yr="2000 -Current" |
| 158 | 138 or 157 |
| 159 | limit 158 to yr="2000 - 2010" |
| 160 | remove duplicates from 159 |
| 161 | limit 158 to yr="2011 -Current" |
| 162 | remove duplicates from 161 |
| 163 | 160 or 162 |
| **Research Question 1 (Clinical Effectiveness; Focused on: Risk-Based Screening, Prevalence-Based Screening):** | |
| 1 | Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/ or Hepatitis C Antibodies/ or exp Hepatitis C Antigens/ |
| 2 | (hepatitis C or hepC or hep C or hepacivirus* or HCV).ti,ab,kf. |
| 3 | 1 or 2 |
| 4 | (opportunistic adj2 (screen* or detect or detection or test or testing or tests)).ti,ab,kf. |
| 5 | (universal adj2 (screen* or detect or detection or test or testing or tests)).ti,ab,kf. |
| 6 | ((individual or group or public or formal or informal or ongoing exposure or active or spontaneous or proactive* or preemptiv* or community or communities or open or widespread or organised or organized or target* or population focused or specific population or population based or group specific or group based or first line) adj2 (screen* or detect or detection or test or tests or testing) adj2 (program* or service or services |

| MULTI-DATABASE STRATEGY: RESEARCH QUESTIONS 1 TO 4 | |
|---|---|
| | or pathway* or path way or path ways)).ti,ab,kf. |
| 7 | ((behaviour* or behavior* or risk or risks or riskbased* or prevalence) adj2 (screen*or detect or detection or test or testing or tests)).ti,ab,kf. |
| 8 | ((primary care or point of care or POC or ER or ED or emergency department or emergency room) adj2 (screen*or detect or detection or test or testing or tests)).ti,ab,kf. |
| 9 | (screen* adj3 (test or testing) adj3 (antibody or antibodies)).ti,ab,kf. |
| 10 | 4 or 5 or 6 or 7 or 8 or 9 |
| 11 | 3 and 10 |
| 12 | exp hepatitis C/ or exp Hepatitis C virus/ or exp hepatitis C antibody/ or exp hepatitis C antigen/ |
| 13 | 2 or 12 |
| 14 | 10 and 13 |
| 15 | 11 use pmez |
| 16 | 14 use oemezd |
| 17 | 15 or 16 |
| 18 | limit 17 to yr="2000 -Current" |
| 19 | limit 18 to english language |
| 20 | limit 19 to french |
| 21 | 19 or 20 |
| 22 | remove duplicates from 21 |
| 23 | 22 not conference abstract.pt |
| **Research Question 1 (Clinical Effectiveness; Focused on: EIA Screening):** | |
| 1 | Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/ or Hepatitis C Antibodies/ or exp Hepatitis C Antigens/ |
| 2 | (hepatitis C or hepC or hep C or hepacivirus* or HCV).ti,ab,kf. |
| 3 | 1 or 2 |
| 4 | exp Mass screening/ |
| 5 | (detect or detection or screen or screens or screened or screening).ti,ab,kf. |
| 6 | 4 or 5 |
| 7 | 3 and 6 |
| 8 | meta-analysis.pt. |
| 9 | meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ |
| 10 | ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab. |
| 11 | ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab. |
| 12 | ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab. |
| 13 | (data synthes* or data extraction* or data abstraction*).ti,ab. |
| 14 | (handsearch* or hand search*).ti,ab. |
| 15 | (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab. |
| 16 | (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab. |
| 17 | (meta regression* or metaregression*).ti,ab. |
| 18 | (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw. |
| 19 | (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw. |

| MULTI-DATABASE STRATEGY: RESEARCH QUESTIONS 1 TO 4 | |
|---|---|
| 20 | (cochrane or (health adj2 technology assessment) or evidence report).jw. |
| 21 | (meta-analysis or systematic review).md. |
| 22 | (comparative adj3 (efficacy or effectiveness)).ti,ab. |
| 23 | (outcomes research or relative effectiveness).ti,ab. |
| 24 | ((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab. |
| 25 | or/8-24 |
| 26 | (Randomized Controlled Trial or Controlled Clinical Trial).pt. |
| 27 | (Clinical Trial or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt. |
| 28 | Multicenter Study.pt. |
| 29 | Randomized Controlled Trial/ |
| 30 | Randomized Controlled Trials as Topic/ |
| 31 | "Randomized Controlled Trial (topic)"/ |
| 32 | Controlled Clinical Trial/ |
| 33 | Controlled Clinical Trials as Topic/ |
| 34 | "Controlled Clinical Trial (topic)"/ |
| 35 | Clinical Trial/ or Phase 2 Clinical Trial/ or Phase 3 Clinical Trial/ or Phase 4 Clinical Trial/ |
| 36 | Clinical Trials as Topic/ or Clinical Trials, Phase II as Topic/ or Clinical Trials, Phase III as Topic/ or Clinical Trials, Phase IV as Topic/ |
| 37 | "Clinical Trial (topic)"/ or "Phase 2 Clinical Trial (topic)"/ or "Phase 3 Clinical Trial (topic)"/ or "Phase 4 Clinical Trial (topic)"/ |
| 38 | Multicenter Study/ or Multicenter Study as Topic/ or "Multicenter Study (topic)"/ |
| 39 | Randomization/ |
| 40 | Random Allocation/ |
| 41 | Double-Blind Method/ |
| 42 | Double Blind Procedure/ |
| 43 | Double-Blind Studies/ |
| 44 | Single-Blind Method/ |
| 45 | Single Blind Procedure/ |
| 46 | Single-Blind Studies/ |
| 47 | Placebos/ |
| 48 | Placebo/ |
| 49 | Control Groups/ |
| 50 | Control Group/ |
| 51 | Cross-Over Studies/ or Crossover Procedure/ |
| 52 | (random* or sham or placebo*).ti,ab,hw. |
| 53 | ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw. |
| 54 | ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw. |
| 55 | (control* adj3 (study or studies or trial*)).ti,ab,hw. |
| 56 | (clinical adj3 (study or studies or trial*)).ti,ab,hw. |
| 57 | (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw. |
| 58 | (phase adj3 (study or studies or trial*)).ti,ab,hw. |
| 59 | ((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw. |
| 60 | ((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw. |

| MULTI-DATABASE STRATEGY: RESEARCH QUESTIONS 1 TO 4 | |
|---|---|
| 61 | allocated.ti,ab,hw. |
| 62 | ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw. |
| 63 | trial.ti. |
| 64 | or/26-63 |
| 65 | exp animals/ |
| 66 | exp animal experimentation/ |
| 67 | exp models animal/ |
| 68 | exp animal experiment/ |
| 69 | nonhuman/ |
| 70 | exp vertebrate/ |
| 71 | animal.po. |
| 72 | or/65-71 |
| 73 | exp humans/ |
| 74 | exp human experiment/ |
| 75 | human.po. |
| 76 | or/73-75 |
| 77 | 72 not 76 |
| 78 | 64 not 77 |
| 79 | epidemiologic methods.sh. |
| 80 | epidemiologic studies.sh. |
| 81 | cohort studies/ |
| 82 | cohort analysis/ |
| 83 | longitudinal studies/ |
| 84 | longitudinal study/ |
| 85 | prospective studies/ |
| 86 | prospective study/ |
| 87 | follow-up studies/ |
| 88 | follow up/ |
| 89 | followup studies/ |
| 90 | retrospective studies/ |
| 91 | retrospective study/ |
| 92 | case-control studies/ |
| 93 | exp case control study/ |
| 94 | cross-sectional study/ |
| 95 | observational study/ |
| 96 | quasi experimental methods/ |
| 97 | quasi experimental study/ |
| 98 | validation studies.pt. |
| 99 | (observational adj3 (study or studies or design or analysis or analyses)).ti,ab. |
| 100 | cohort*.ti,ab. |
| 101 | (prospective adj7 (study or studies or design or analysis or analyses or cohort)).ti,ab. |
| 102 | ((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab. |

| MULTI-DATABASE STRATEGY: RESEARCH QUESTIONS 1 TO 4 | |
|---|---|
| 103 | ((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data or cohort)).ti,ab. |
| 104 | (retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).ti,ab. |
| 105 | ((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab. |
| 106 | (case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab. |
| 107 | (population adj3 (study or studies or analysis or analyses)).ti,ab. |
| 108 | (descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab. |
| 109 | ((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab. |
| 110 | (cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab. |
| 111 | ((natural adj experiment) or (natural adj experiments)).ti,ab. |
| 112 | (quasi adj (experiment or experiments or experimental)).ti,ab. |
| 113 | ((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab. |
| 114 | (prevalence adj3 (study or studies or analysis or analyses)).ti,ab. |
| 115 | case series.ti,ab. |
| 116 | case reports.pt. |
| 117 | case report/ |
| 118 | case study/ |
| 119 | (case adj3 (report or reports or study or studies or histories)).ti,ab. |
| 120 | organizational case studies.sh. |
| 121 | or/79-120 |
| 122 | (disease adj2 (progress* or predict* or prognosis) adj2 (Outcome* or Risk* or Model*)).ti,ab,kf. |
| 123 | (Predict* adj2 (Outcome* or Risk* or Model*)).ti,ab,kf. |
| 124 | ((History or Variable* or Criteria or Scor* or Characteristic* or Finding* or Factor*) adj2 (Predict* or Model* or Decision* or Identif* or Prognos*)).ti,ab,kf. |
| 125 | Decision*.ti,ab,kf. and *Logistic Models/ |
| 126 | ((Prognostic or prognostic) adj2 (History or Variable* or Criteria or Scor* or Characteristic* or Finding* or Factor* or Model*)).ti,ab,kf. |
| 127 | Disease model*.ti,ab,kf. |
| 128 | 122 or 123 or 124 or 125 or 126 or 127 |
| 129 | exp Enzyme-Linked Immunosorbent Assay/ |
| 130 | (ELISA or EIA or enzyme immunoassa* or enzyme linked immunosorben* or enzyme linked immunoassa* or enzyme linked immuno-sorben* or enzyme linked immunoblot*).ti,ab,kf. |
| 131 | ((immunosorb* or immuno-sorb*) adj2 enzyme* adj2 (assay or assays)).ti,ab,kf. |
| 132 | (Index test or index tests or index standard).ti,ab,kf. |
| 133 | 129 or 130 or 131 or 132 |
| 134 | 7 and 133 |
| 135 | 134 and 25 |
| 136 | 134 and 78 |
| 137 | 134 and 121 |
| 138 | 134 and 128 |
| 139 | 135 or 136 or 137 or 138 |
| 140 | exp hepatitis C/ or exp Hepatitis C virus/ or exp hepatitis C antibody/ or exp hepatitis C antigen/ |

| MULTI-DATABASE STRATEGY: RESEARCH QUESTIONS 1 TO 4 | |
|---|---|
| 141 | 2 or 140 |
| 142 | exp antibody screening/ or exp mass screening/ or exp screening/ or exp screening test/ |
| 143 | 5 or 142 |
| 144 | 141 and 143 |
| 145 | exp enzyme linked immunosorbent assay/ |
| 146 | 130 or 131 or 132 or 145 |
| 147 | 144 and 146 |
| 148 | 147 use oemezd |
| 149 | 147 and 25 |
| 150 | 147 and 78 |
| 151 | 147 and 121 |
| 152 | 147 and 128 |
| 153 | 149 or 150 or 151 or 152 |
| 154 | 139 use pmez |
| 155 | 153 or 154 |
| 156 | limit 155 to yr="2000 -Current" |
| 157 | limit 156 to english language |
| 158 | limit 156 to french |
| 159 | 157 or 158 |
| 160 | remove duplicates from 159 |
| 161 | 160 not conference abstract.pt |
| **Research Question 2 (Harms):** | |
| 1 | *Hepatitis C/ or *Hepatitis C, Chronic/ or *Hepacivirus/ or *Hepatitis C Antibodies/ or exp *Hepatitis C Antigens/ |
| 2 | (hepatitis C or hepC or hep C or hepacivirus* or HCV).ti,kf. |
| 3 | 1 or 2 |
| 4 | exp *Mass screening/ |
| 5 | (detect or detection or screen or screens or screened or screening).ti,kf. |
| 6 | 4 or 5 |
| 7 | 3 and 6 |
| 8 | exp safety/ |
| 9 | equipment safety/ |
| 10 | exp equipment failure/ |
| 11 | consumer product safety/ |
| 12 | "product recalls and withdrawals"/ |
| 13 | medical device recalls/ |
| 14 | "safety-based medical device withdrawals"/ |
| 15 | product surveillance, postmarketing/ |
| 16 | postmarketing surveillance/ |
| 17 | clinical trial, phase iv.pt. |
| 18 | phase 4 clinical trial/ |
| 19 | clinical trials, phase iv as topic/ |

| MULTI-DATABASE STRATEGY: RESEARCH QUESTIONS 1 TO 4 | |
|---|---|
| 20 | "phase 4 clinical trial (topic)"/ |
| 21 | exp postoperative complications/ |
| 22 | exp postoperative complication/ |
| 23 | exp intraoperative complications/ |
| 24 | peroperative complication/ |
| 25 | exp side effect/ |
| 26 | "side effects (treatment)"/ |
| 27 | (hazard* or defect* or misuse* or failure* or malfunction* or error*).ti. |
| 28 | (safe* or adverse* or undesirable or harm* or injurious or risk or risks or reaction* or complication* or poison*).ti. |
| 29 | (side effect* or safety or unsafe).ti,ab. |
| 30 | ((adverse or undesirable or harm* or toxic or injurious or serious or fatal) adj3 (effect* or reaction* or event* or outcome* or incident*)).ab. |
| 31 | (toxic or toxicit* or toxologic* or intoxication or noxious or tolerability or teratogen*).ti,ab. |
| 32 | (warning* or recall* or withdrawn* or withdrawal*).ti. |
| 33 | (death or deaths or fatal or fatality or fatalities).ti. |
| 34 | or/8-33 |
| 35 | exp Enzyme-Linked Immunosorbent Assay/ae, px [Adverse Effects, Psychology] |
| 36 | exp Disclosure/ or exp Self Disclosure/ or exp Ethics/ or social support/ or *privacy/ or exp *Sociology/ or exp Psychology, Social/ |
| 37 | (overdiagnos* or over diagnos* or overtreat* or misdiagnose*).ti,ab,kf. |
| 38 | ((over or unnecessar* or execess*) adj2 (treat* or test* or procedure*)).ti,ab,kf. |
| 39 | (stress or stressor* or anxious or anxiety or descriminat* or stigma* or violence or violent or social or harm or harms or anxiety or anxieties or threat or threatening or threatened).ti,ab,kf. |
| 40 | (psychological or psycholog* or psychosocial or preference* or motivation* or intention* or behaviour* or behavior* or attitude* or moral or morals or morality or ethics or ethical or bioethic* or genethic* or confidential* or disclosure* or communication or acceptance or accepting or adjustment or ethic* or moral* or privacy).ti. |
| 41 | ((care or treatment or presumed) adj2 (duty or obligat* or consent)).ti. |
| 42 | (inform* adj (choice* or decision* or consent)).ti. |
| 43 | (social adj (responsib* or obligat*)).ti. |
| 44 | (legal* or liabilit* or litigation* or constitutional or justice or law or laws or jurisprudence or complicit*).ti. |
| 45 | human right*.ti,ab,kf. |
| 46 | civil right*.ti,ab,kf. |
| 47 | (prejudice* or inequalit* or fairness).ti,ab,kf. |
| 48 | ((care or treatment) adj2 (duty or obligat*)).ti,ab,kf. |
| 49 | (social* adj (responsibl* or obligat*)).ti,ab,kf. |
| 50 | (communitarian* or beneficence or nonmaleficence or non-maleficence or accountability).ti,ab,kf. |
| 51 | or/35-50 |
| 52 | 7 and 34 |
| 53 | 7 and 35 |
| 54 | 7 and 51 |
| 55 | 52 or 53 or 54 |
| 56 | 55 use pmez |

| MULTI-DATABASE STRATEGY: RESEARCH QUESTIONS 1 TO 4 | |
|---|---|
| 57 | exp hepatitis C/ or exp Hepatitis C virus/ or exp hepatitis C antibody/ or exp hepatitis C antigen/ |
| 58 | 2 or 57 |
| 59 | exp antibody screening/ or exp mass screening/ or exp screening/ or exp screening test/ |
| 60 | 5 or 59 |
| 61 | 58 and 60 |
| 62 | enzyme linked immunosorbent assay/ae [Adverse Drug Reaction] |
| 63 | 34 or 51 or 62 |
| 64 | 61 and 63 |
| 65 | 64 use oemezd |
| 66 | 56 or 65 |
| 67 | 66 not conference abstract.pt. |
| 68 | limit 67 to english language |
| 69 | limit 67 to french |
| 70 | 68 or 69 |
| 71 | limit 70 to yr="2000 -Current" |
| 72 | remove duplicates from 71 |
| **Research Question 3 (Cost-Effectiveness):** | |
| 1 | Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/ or Hepatitis C Antibodies/ or exp Hepatitis C Antigens/ |
| 2 | (hepatitis C or hepC or hep C or hepacivirus* or HCV).ti,ab,kf. |
| 3 | 1 or 2 |
| 4 | exp Mass screening/ |
| 5 | (detect or detection or screen or screens or screened or screening).ti,ab,kf. |
| 6 | 4 or 5 |
| 7 | 3 and 6 |
| 8 | Economics/ |
| 9 | exp "Costs and Cost Analysis"/ |
| 10 | Economics, Nursing/ |
| 11 | Economics, Medical/ |
| 12 | Economics, Pharmaceutical/ |
| 13 | exp Economics, Hospital/ |
| 14 | Economics, Dental/ |
| 15 | exp "Fees and Charges"/ |
| 16 | exp Budgets/ |
| 17 | budget*.ti,ab. |
| 18 | (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti. |
| 19 | (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 |
| 20 | (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab. |
| 21 | (value adj2 (money or monetary)).ti,ab. |
| 22 | exp models, economic/ |

| MULTI-DATABASE STRATEGY: RESEARCH QUESTIONS 1 TO 4 | |
|---|---|
| 23 | economic model*.ti,ab. |
| 24 | markov chains/ |
| 25 | markov.ti,ab. |
| 26 | monte carlo method/ |
| 27 | monte carlo.ti,ab. |
| 28 | exp Decision Theory/ |
| 29 | (decision* adj2 (tree* or analy* or model*)).ti,ab. |
| 30 | or/8-29 |
| 31 | "Value of Life"/ |
| 32 | Quality of Life/ |
| 33 | quality of life.ti. |
| 34 | ((instrument or instruments) adj3 quality of life).ab. |
| 35 | Quality-Adjusted Life Years/ |
| 36 | quality adjusted life.ti,ab. |
| 37 | (qaly* or qald* or qale* or qtime* or life year or life years).ti,ab. |
| 38 | disability adjusted life.ti,ab. |
| 39 | daly*.ti,ab. |
| 40 | (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab. |
| 41 | (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab. |
| 42 | (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab. |
| 43 | (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab. |
| 44 | (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab. |
| 45 | (hql or hqol or h qol or hrqol or hr qol).ti,ab. |
| 46 | (hye or hyes).ti,ab. |
| 47 | (health* adj2 year* adj2 equivalent*).ti,ab. |
| 48 | (pqol or qls).ti,ab. |
| 49 | (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab. |
| 50 | nottingham health profile*.ti,ab. |
| 51 | sickness impact profile.ti,ab. |
| 52 | exp health status indicators/ |
| 53 | (health adj3 (utilit* or status)).ti,ab. |
| 54 | (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab. |
| 55 | (preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab. |
| 56 | disutilit*.ti,ab. |
| 57 | rosser.ti,ab. |
| 58 | willingness to pay.ti,ab. |
| 59 | standard gamble*.ti,ab. |
| 60 | (time trade off or time tradeoff).ti,ab. |

| MULTI-DATABASE STRATEGY: RESEARCH QUESTIONS 1 TO 4 | |
|---|---|
| 61 | tto.ti,ab. |
| 62 | (hui or hui1 or hui2 or hui3).ti,ab. |
| 63 | (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab. |
| 64 | duke health profile.ti,ab. |
| 65 | functional status questionnaire.ti,ab. |
| 66 | dartmouth coop functional health assessment*.ti,ab. |
| 67 | or/31-66 |
| 68 | exp Canada/ |
| 69 | (canadian* or canada* or british columbia* or alberta* or saskatchewan* or manitoba* or ontario* or quebec* or new brunswick* or prince edward island* or nova scotia* or labrador* or newfoundland* or nunavut* or northwest territor* or yukon* or toronto* or montreal* or vancouver* or ottawa* or calgary* or edmonton* or winnipeg* or first nation* or metis).ti,ab,hw. |
| 70 | (canadian* or canada* or british columbia* or alberta* or saskatchewan* or manitoba* or ontario* or quebec* or new brunswick* or prince edward island* or nova scotia* or labrador* or newfoundland* or nunavut* or northwest territor* or yukon* or toronto* or montreal* or vancouver* or ottawa* or calgary* or edmonton* or winnipeg* or first nation* or metis).jw,jx. |
| 71 | canada.lo. |
| 72 | (canadian* or canada* or british columbia* or alberta* or saskatchewan* or manitoba* or ontario* or quebec* or new brunswick* or prince edward island* or nova scotia* or labrador* or newfoundland* or nunavut* or northwest territor* or yukon* or toronto* or montreal* or vancouver* or ottawa* or calgary* or edmonton* or winnipeg* or first nation* or metis).sd,ss,if,cr. |
| 73 | or/68-72 |
| 74 | 7 and 73 |
| 75 | 30 and 74 |
| 76 | 67 and 74 |
| 77 | 75 or 76 |
| 78 | limit 77 to english language |
| 79 | limit 77 to french |
| 80 | 78 or 79 |
| 81 | 80 use pmez |
| 82 | exp hepatitis C/ or exp Hepatitis C virus/ or exp hepatitis C antibody/ or exp hepatitis C antigen/ |
| 83 | 82 or 2 |
| 84 | exp antibody screening/ or exp mass screening/ or exp screening/ or exp screening test/ |
| 85 | 84 or 5 |
| 86 | 83 and 85 |
| 87 | socioeconomics/ |
| 88 | exp Quality of Life/ |
| 89 | quality of life.ti. |
| 90 | ((instrument or instruments) adj3 quality of life).ab. |
| 91 | Quality-Adjusted Life Year/ |
| 92 | quality adjusted life.ti,ab. |
| 93 | (qaly* or qald* or qale* or qtime* or life year or life years).ti,ab. |
| 94 | disability adjusted life.ti,ab. |
| 95 | daly*.ti,ab. |

| MULTI-DATABASE STRATEGY: RESEARCH QUESTIONS 1 TO 4 | |
|---|---|
| 96 | (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab. |
| 97 | (sf6 or sf 6 or short form 6 or shortform 6 or sf6d or sf 6d or short form 6d or shortform 6d or sf six or sfsix or shortform six or short form six).ti,ab. |
| 98 | (sf8 or sf 8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab. |
| 99 | (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab. |
| 100 | (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab. |
| 101 | (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab. |
| 102 | (hql or hqol or h qol or hrqol or hr qol).ti,ab. |
| 103 | (hye or hyes).ti,ab. |
| 104 | (health* adj2 year* adj2 equivalent*).ti,ab. |
| 105 | (pqol or qls).ti,ab. |
| 106 | (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab. |
| 107 | nottingham health profile*.ti,ab. |
| 108 | nottingham health profile/ |
| 109 | sickness impact profile.ti,ab. |
| 110 | sickness impact profile/ |
| 111 | health status indicator/ |
| 112 | (health adj3 (utilit* or status)).ti,ab. |
| 113 | (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab. |
| 114 | (preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab. |
| 115 | disutilit*.ti,ab. |
| 116 | rosser.ti,ab. |
| 117 | willingness to pay.ti,ab. |
| 118 | standard gamble*.ti,ab. |
| 119 | (time trade off or time tradeoff).ti,ab. |
| 120 | tto.ti,ab. |
| 121 | (hui or hui1 or hui2 or hui3).ti,ab. |
| 122 | (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab. |
| 123 | duke health profile.ti,ab. |
| 124 | functional status questionnaire.ti,ab. |
| 125 | dartmouth coop functional health assessment*.ti,ab. |
| 126 | or/87-125 |
| 127 | socioeconomics/ |
| 128 | exp Quality of Life/ |
| 129 | quality of life.ti. |
| 130 | ((instrument or instruments) adj3 quality of life).ab. |
| 131 | Quality-Adjusted Life Year/ |
| 132 | quality adjusted life.ti,ab. |
| 133 | (qaly* or qald* or qale* or qtime* or life year or life years).ti,ab. |

| MULTI-DATABASE STRATEGY: RESEARCH QUESTIONS 1 TO 4 | |
|---|---|
| 134 | disability adjusted life.ti,ab. |
| 135 | daly*.ti,ab. |
| 136 | (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab. |
| 137 | (sf6 or sf 6 or short form 6 or shortform 6 or sf6d or sf 6d or short form 6d or shortform 6d or sf six or sfsix or shortform six or short form six).ti,ab. |
| 138 | (sf8 or sf 8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab. |
| 139 | (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab. |
| 140 | (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab. |
| 141 | (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab. |
| 142 | (hql or hqol or h qol or hrqol or hr qol).ti,ab. |
| 143 | (hye or hyes).ti,ab. |
| 144 | (health* adj2 year* adj2 equivalent*).ti,ab. |
| 145 | (pqol or qls).ti,ab. |
| 146 | or/127-145 |
| 147 | 86 and 126 |
| 148 | 86 and 146 |
| 149 | 147 or 148 |
| 150 | 73 and 149 |
| 151 | 150 use oemezd |
| 152 | 81 or 151 |
| 153 | limit 152 to yr="2000 - 2015" |
| 154 | limit 153 to english language |
| 155 | limit 153 to french |
| 156 | 154 or 155 |
| 157 | 156 not conference abstract.pt. |
| 158 | remove duplicates from 167 |
| **Research Question 4 (Patients' Preferences):** | |
| 1 | Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/ or Hepatitis C Antibodies/ or exp Hepatitis C Antigens/ |
| 2 | (hepatitis C or hepC or hep C or hepacivirus* or HCV).ti,ab,kf. |
| 3 | 1 or 2 |
| 4 | exp Mass screening/ |
| 5 | (detect or detection or screen or screens or screened or screening).ti,ab,kf. |
| 6 | 4 or 5 |
| 7 | 3 and 6 |
| 8 | meta-analysis.pt. |
| 9 | meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ |
| 10 | ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab. |
| 11 | ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab. |
| 12 | ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 |

| MULTI-DATABASE STRATEGY: RESEARCH QUESTIONS 1 TO 4 | |
|---|---|
| | analy*)).ti,ab. |
| 13 | (data synthes* or data extraction* or data abstraction*).ti,ab. |
| 14 | (handsearch* or hand search*).ti,ab. |
| 15 | (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab. |
| 16 | (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab. |
| 17 | (meta regression* or metaregression*).ti,ab. |
| 18 | (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw. |
| 19 | (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw. |
| 20 | (cochrane or (health adj2 technology assessment) or evidence report).jw. |
| 21 | (meta-analysis or systematic review).md. |
| 22 | (comparative adj3 (efficacy or effectiveness)).ti,ab. |
| 23 | (outcomes research or relative effectiveness).ti,ab. |
| 24 | ((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab. |
| 25 | or/8-24 |
| 26 | (Randomized Controlled Trial or Controlled Clinical Trial).pt. |
| 27 | (Clinical Trial or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt. |
| 28 | Multicenter Study.pt. |
| 29 | Randomized Controlled Trial/ |
| 30 | Randomized Controlled Trials as Topic/ |
| 31 | "Randomized Controlled Trial (topic)"/ |
| 32 | Controlled Clinical Trial/ |
| 33 | Controlled Clinical Trials as Topic/ |
| 34 | "Controlled Clinical Trial (topic)"/ |
| 35 | Clinical Trial/ or Phase 2 Clinical Trial/ or Phase 3 Clinical Trial/ or Phase 4 Clinical Trial/ |
| 36 | Clinical Trials as Topic/ or Clinical Trials, Phase II as Topic/ or Clinical Trials, Phase III as Topic/ or Clinical Trials, Phase IV as Topic/ |
| 37 | "Clinical Trial (topic)"/ or "Phase 2 Clinical Trial (topic)"/ or "Phase 3 Clinical Trial (topic)"/ or "Phase 4 Clinical Trial (topic)"/ |
| 38 | Multicenter Study/ or Multicenter Study as Topic/ or "Multicenter Study (topic)"/ |
| 39 | Randomization/ |
| 40 | Random Allocation/ |
| 41 | Double-Blind Method/ |
| 42 | Double Blind Procedure/ |
| 43 | Double-Blind Studies/ |
| 44 | Single-Blind Method/ |
| 45 | Single Blind Procedure/ |
| 46 | Single-Blind Studies/ |
| 47 | Placebos/ |
| 48 | Placebo/ |
| 49 | Control Groups/ |
| 50 | Control Group/ |

| MULTI-DATABASE STRATEGY: RESEARCH QUESTIONS 1 TO 4 | |
|---|---|
| 51 | Cross-Over Studies/ or Crossover Procedure/ |
| 52 | (random* or sham or placebo*).ti,ab,hw. |
| 53 | ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw. |
| 54 | ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw. |
| 55 | (control* adj3 (study or studies or trial*)).ti,ab,hw. |
| 56 | (clinical adj3 (study or studies or trial*)).ti,ab,hw. |
| 57 | (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw. |
| 58 | (phase adj3 (study or studies or trial*)).ti,ab,hw. |
| 59 | ((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw. |
| 60 | ((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw. |
| 61 | allocated.ti,ab,hw. |
| 62 | ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw. |
| 63 | trial.ti. |
| 64 | or/26-63 |
| 65 | exp animals/ |
| 66 | exp animal experimentation/ |
| 67 | exp models animal/ |
| 68 | exp animal experiment/ |
| 69 | nonhuman/ |
| 70 | exp vertebrate/ |
| 71 | animal.po. |
| 72 | or/65-71 |
| 73 | exp humans/ |
| 74 | exp human experiment/ |
| 75 | human.po. |
| 76 | or/73-75 |
| 77 | 72 not 76 |
| 78 | 64 not 77 |
| 79 | epidemiologic methods.sh. |
| 80 | epidemiologic studies.sh. |
| 81 | cohort studies/ |
| 82 | cohort analysis/ |
| 83 | longitudinal studies/ |
| 84 | longitudinal study/ |
| 85 | prospective studies/ |
| 86 | prospective study/ |
| 87 | follow-up studies/ |
| 88 | follow up/ |
| 89 | followup studies/ |
| 90 | retrospective studies/ |
| 91 | retrospective study/ |
| 92 | case-control studies/ |

| MULTI-DATABASE STRATEGY: RESEARCH QUESTIONS 1 TO 4 | |
|---|---|
| 93 | exp case control study/ |
| 94 | cross-sectional study/ |
| 95 | observational study/ |
| 96 | quasi experimental methods/ |
| 97 | quasi experimental study/ |
| 98 | validation studies.pt. |
| 99 | (observational adj3 (study or studies or design or analysis or analyses)).ti,ab. |
| 100 | cohort*.ti,ab. |
| 101 | (prospective adj7 (study or studies or design or analysis or analyses or cohort)).ti,ab. |
| 102 | ((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab. |
| 103 | ((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data or cohort)).ti,ab. |
| 104 | (retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).ti,ab. |
| 105 | ((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab. |
| 106 | (case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab. |
| 107 | (population adj3 (study or studies or analysis or analyses)).ti,ab. |
| 108 | (descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab. |
| 109 | ((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab. |
| 110 | (cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab. |
| 111 | ((natural adj experiment) or (natural adj experiments)).ti,ab. |
| 112 | (quasi adj (experiment or experiments or experimental)).ti,ab. |
| 113 | ((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab. |
| 114 | (prevalence adj3 (study or studies or analysis or analyses)).ti,ab. |
| 115 | case series.ti,ab. |
| 116 | case reports.pt. |
| 117 | case report/ |
| 118 | case study/ |
| 119 | (case adj3 (report or reports or study or studies or histories)).ti,ab. |
| 120 | organizational case studies.sh. |
| 121 | or/79-120 |
| 122 | exp patient acceptance of health care/ or exp Attitude to Health/ or exp Attitude/ or exp Attitude to Death/ or Health Behavior/ or exp Illness Behavior/ |
| 123 | ((patient or patients or proband* or individuals or survivor* or family or families or familial or kindred* or relative or relatives or care giver* or caregiver* or carer or carers) and (attitude or attitudes or preference* or input or experience or experiences or value or values or perspective* or expectation* or choice* or choose* or choosing or "day-to-day" or participat* or acceptance or symptom or symptoms or limitations or survey* or focus group* or lives or interview* or quality of life or satisfaction or burden or attitude* or knowledge or lessons or reaction* or motivation* or intention* or involv* or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding)).ti,ab,kf. |
| 124 | (heuristic* or attitude or attitudes preference* or input or experience or experiences or value or values or perspective* or expectation* or choice* or choose* or choosing or "day-to-day" or participat* or acceptance or limitations or survey* or focus group* or lives or interview* or quality of life or satisfaction or burden or attitude* or knowledge or lessons or reaction* or motivation* or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding).ab. /freq=2 |

| MULTI-DATABASE STRATEGY: RESEARCH QUESTIONS 1 TO 4 | |
|---|---|
| 125 | patient*.jw. |
| 126 | 122 or 123 or 124 or 125 |
| 127 | 7 and 126 |
| 128 | 121 and 127 |
| 129 | 25 and 127 |
| 130 | 78 and 127 |
| 131 | 128 or 129 or 130 |
| 132 | 131 use pmez |
| 133 | exp hepatitis C/ or exp Hepatitis C virus/ or exp hepatitis C antibody/ or exp hepatitis C antigen/ |
| 134 | 133 or 2 |
| 135 | exp antibody screening/ or exp mass screening/ or exp screening/ or exp screening test/ |
| 136 | 135 or 5 |
| 137 | 134 and 136 |
| 138 | exp attitude to health/ or attitude/ or attitude to illness/ or exp attitude to death/ or exp health behavior/ or exp illness behavior/ |
| 139 | 123 or 124 or 125 or 138 |
| 140 | 137 and 139 |
| 141 | 140 and 25 |
| 142 | 140 and 78 |
| 143 | 140 and 121 |
| 144 | 141 or 142 or 143 |
| 145 | 144 use oemezd |
| 146 | 132 or 145 |
| 147 | limit 146 to yr="2000 -Current" |
| 148 | limit 147 to english language |
| 149 | limit 147 to french |
| 150 | 148 or 149 |
| 151 | 150 not conference abstract.pt. |
| 152 | remove duplicates from 151 |

**Grey Literature**

| | |
|---|---|
| Dates for Search: | November 2015 |
| Keywords: | Included terms for hepatitis, hepatitis screening, screening methods, screening tests (focused on ELISA) |
| Limits: | Publication years 2000 onward |

Relevant websites from the following sections of the CADTH grey literature checklist *Grey matters: a practical tool for evidence-based searching*[111] were searched:

- health technology assessment agencies
- health economics
- clinical practice guidelines
- databases (free)
- Internet search.

| OVERVIEW: LITERATURE SEARCH STRATEGY FOR RESEARCH QUESTION 5 | |
|---|---|
| Interface: | Ovid |
| Databases: | Ovid MEDLINE In-Process & Other Non-Indexed Citations<br>Embase 1974 to 2015 April 1 |
| Date of Search: | April 1, 2016 |
| Alerts: | Bi-weekly search alerts will be run |
| Study Types: | Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials and non-randomized studies |
| Limits: | English and French language |
| **SYNTAX GUIDE** | |
| MeSH | Medical Subject Heading |
| Exp | Explode a subject heading |
| * | Before a word, indicates that the marked subject heading is a primary topic;<br>or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings |
| # | Truncation symbol for one character |
| ADJ | Requires words are adjacent to each other (in any order) |
| ADJ# | Adjacency within # number of words (in any order) |
| .ti | Title |
| .ab | Abstract |
| .pt<br>.kf | Publication type<br>Author-provided keyword |

| MULTI-DATABASE STRATEGY: RESEARCH QUESTION 5 | |
|---|---|
| **Research Question 5: Antibody Tests** | |
| 1 | Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/ or Hepatitis C Antibodies/ or exp Hepatitis C Antigens/ |
| 2 | (hepatitis C or hepC or hep C or hepacivirus* or HCV).ti,ab,kf,kw. |
| 3 | 1 or 2 |
| 4 | exp Mass screening/ |
| 5 | (detect or detection or screen or screens or screened or screening).ti,ab,kf,kw. |
| 6 | 4 or 5 |
| 7 | 3 and 6 |
| 8 | 7 use ppez |
| 9 | exp Enzyme-Linked Immunosorbent Assay/ |
| 10 | (ELISA or EIA or enzyme immunoassa* or enzyme linked immunosorben* or enzyme linked immunoassa* or enzyme linked immuno-sorben* or enzyme linked immunoblot* or monolisa).ti,ab,kf,kw. |
| 11 | ((immunosorb* or immuno-sorb*) adj3 enzyme* adj3 (assay or assays immunoassay or immunoassays)).ti,ab,kf,kw. |
| 12 | (Index test or index tests or index standard).ti,ab,kf,kw. |
| 13 | exp Immunoassay/ |
| 14 | ((immunosorb* or immuno-sorb*) adj3 enzyme*).ti,ab,kf,kw. |
| 15 | 13 and 14 |
| 16 | ((murex or Ultra or BioRad or Ortho) adj3 HCV).ti,ab,kf,kw. |
| 17 | ((immunoassay or immunoassays) adj3 enzyme*).ti,ab,kf,kw. |

| MULTI-DATABASE STRATEGY: RESEARCH QUESTION 5 | |
|---|---|
| 18 | 9 or 10 or 11 or 12 or 15 or 16 or 17 |
| 19 | 18 use ppez |
| 20 | MEIA.ti,ab,kf,kw. |
| 21 | Microparticle based enzyme immunoass*.ti,ab,kf,kw. |
| 22 | ((microparticle* or micro particle*) adj3 enzyme* adj3 (assay or assays or immunoassay or immunoassays)).ti,ab,kf,kw. |
| 23 | ((Microparticle* or micro particle*) adj3 (EIA or ELISA)).ti,ab,kf,kw. |
| 24 | 13 and 23 |
| 25 | AxSym.ti,ab,kf,kw. |
| 26 | 20 or 21 or 22 or 24 or 25 |
| 27 | 26 use ppez |
| 28 | ((chemiluminescen* or luminescenc*) adj3 (assay or assays or immunoassay or immunoassays)).ti,ab,kf,kw. |
| 29 | (Waived adj2 rapid adj2 test*).ti,ab,kf,kw. |
| 30 | (OraQuick or Ora Quick or Architect or Elecsys or Cobas or ADVIA or Centaur or AmpliPrep or Amplicor).ti,ab,kf,kw. |
| 31 | (CLIA or CIA or CLIAwaived or ChLIAs or ECLIA or ECIA or Vitros or INNO-LIA or ECLIA).ti,ab,kf,kw. |
| 32 | (chemiluminescen* or luminescenc*).ti,ab,kf,kw. |
| 33 | 13 and 32 |
| 34 | 28 or 29 or 30 or 31 or 33 |
| 35 | 34 use ppez |
| 36 | ((Chemiluminescence or luminescenc*) adj3 (microparticle* or micro particle*) adj3 (immunoassay or immunoassays or assay or assays)).ti,ab,kf,kw. |
| 37 | CMIA.ti,ab,kf,kw. |
| 38 | ((chemiluminescen* or luminescenc*) adj3 (microparticle* or micro particle*)).ti,ab,kf,kw. |
| 39 | 13 and 38 |
| 40 | (Taqman or Architect).ti,ab,kf,kw. |
| 41 | 36 or 37 or 39 or 40 |
| 42 | 41 use ppez |
| 43 | (RIBA or SIA).ti,ab,kf,kw. |
| 44 | (recombinant adj3 (immunoblot* or immuno blot*) adj3 (assay or assays or immunoassay or immunoassays)).ti,ab,kf,kw. |
| 45 | chiron.ti,ab,kf,kw. |
| 46 | (Strip adj3 immunoblot adj3 (assay or assays)).ti,ab,kf,kw. |
| 47 | 43 or 44 or 45 or 46 |
| 48 | 47 use ppez |
| 49 | ((rapid or quick or point of care or POC or bedside) adj3 (immunoassay or immunoassay)).ti,ab,kf,kw. |
| 50 | exp Point-of-Care Systems/ or exp Point-of-Care Testing/ |
| 51 | (rapid or quick or point of care or POC or bedside).ti,ab,kf. |
| 52 | 50 or 51 |
| 53 | 13 and 52 |
| 54 | (OraQuick or Ora Quick).ti,ab,kf,kw. |
| 55 | 49 or 53 or 54 |
| 56 | 19 or 27 or 35 or 42 or 48 or 55 |

| MULTI-DATABASE STRATEGY: RESEARCH QUESTION 5 | |
|---|---|
| 57 | 8 and 56 |
| 58 | ((screen* or detect*) adj4 (hepatitis C or Hep C or HepC or HCV or HVC) adj4 (test* or diagnostic* or antibody*)).ti,ab,kw,kf. |
| 59 | 57 or 58 |
| 60 | 59 use ppez |
| 61 | "sensitivity and specificity"/ or "limit of detection"/ or roc curve/ or diagnostic errors/ or false negative reactions/ or false positive reactions/ or "Predictive Value of Tests"/ |
| 62 | (Sensitivity or specificity).ti,ab,kf. |
| 63 | (false adj2 (positive* or negative*)).ti,ab,kf. |
| 64 | ((positive* or negative*) adj2 (predictive or likelihood)).ti,ab,kf. |
| 65 | (predictive valu* or validit*).ti,ab,kf. |
| 66 | ((test or tests or testing or tested or diagnostic* or diagnosis) adj2 (performance or accura* or value*)).ti,ab,kf. |
| 67 | (receiver adj2 operating).ti,ab. |
| 68 | (ROC or AUROC* or SROC or HSROC).ti,ab,kf. |
| 69 | ((under or over) adj2 curve).ti,ab,kf. |
| 70 | (detect* adj2 (abilit* or rate*)).ti,ab,kf. |
| 71 | (Significant* adj2 (high or higher or low or lower or associate* or difference* or statistically or correlation*)).ti,ab,kf. |
| 72 | ((gold* or referen*) adj2 standard*).ti,ab,kf. |
| 73 | ((Evaluat* or compar*) adj2 (effica* or usefulness or useful or accura* or diagnostic)).ti,ab,kf. |
| 74 | 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 |
| 75 | 74 use ppez |
| 76 | exp hepatitis C/ or exp Hepatitis C virus/ or exp hepatitis C antibody/ or exp hepatitis C antigen/ |
| 77 | 2 or 76 |
| 78 | exp antibody screening/ or exp mass screening/ or exp screening/ or exp screening test/ |
| 79 | 5 or 78 |
| 80 | 77 and 79 |
| 81 | 80 use oemezd |
| 82 | exp enzyme linked immunosorbent assay/ |
| 83 | 10 or 11 or 12 or 15 or 16 or 17 or 82 |
| 84 | 83 use oemezd |
| 85 | exp microparticle enzyme immunoassay/ |
| 86 | 26 or 85 |
| 87 | 86 use oemezd |
| 88 | exp chemoluminescence/ |
| 89 | 13 and 88 |
| 90 | 34 or 89 |
| 91 | 90 use oemezd |
| 92 | exp Immunoblotting/ |
| 93 | (recombinant adj3 (assay or assays or immunoassay or immunoassays)).ti,ab,kw. |
| 94 | 92 and 93 |
| 95 | 47 or 94 |

| MULTI-DATABASE STRATEGY: RESEARCH QUESTION 5 | |
|---|---|
| 96 | 95 use oemezd |
| 97 | exp chemoluminescence/ or (*chemiluminescen*/ or luminescenc*).ti,ab,kw. |
| 98 | (microparticle* or micro particle*).ti,ab,kw. |
| 99 | 97 and 98 |
| 100 | 99 and 41 |
| 101 | 100 use oemezd |
| 102 | exp "point of care testing"/ |
| 103 | (rapid or quick or point of care or POC or bedside).ti,ab,kw. |
| 104 | 102 or 103 |
| 105 | 13 and 104 |
| 106 | 105 use oemezd |
| 107 | 58 or 84 or 87 or 91 or 96 or 101 or 106 |
| 108 | 107 and 81 |
| 109 | diagnostic accuracy/ or "sensitivity and specificity"/ or "limit of detection"/ or receiver operating characteristic/ or exp diagnostic error/ or predictive value/ or diagnostic value/ or Diagnostic test accuracy study/ |
| 110 | (Sensitivity or specificity).ti,ab,kw. |
| 111 | (false adj2 (positive* or negative*)).ti,ab,kw. |
| 112 | ((positive* or negative*) adj2 (predictive or likelihood)).ti,ab,kw. |
| 113 | (predictive valu* or validit*).ti,ab,kw. |
| 114 | ((test or tests or testing or tested or diagnostic* or diagnosis) adj2 (performance or accura* or value)).ti,ab,kw. |
| 115 | (receiver adj2 operating).ti,ab,kw. |
| 116 | (ROC or AUROC* or SROC or HSROC).ti,ab,kw. |
| 117 | ((under or over) adj2 curve*).ti,ab,kw. |
| 118 | (detect* adj2 (abilit* or rate*)).ti,ab,kw. |
| 119 | (Significant* adj2 (high or higher or low or lower or associate* or difference* or statistically or correlation*)).ti,ab,kw. |
| 120 | ((gold or reference) adj2 standard*).ti,ab,kw. |
| 121 | ((Evaluat* or compar*) adj2 (effica* or usefulness or useful or accurac* or diagnostic)).ti,ab,kw. |
| 122 | 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 |
| 123 | 122 use oemezd |
| 124 | 57 or 108 |
| 125 | 75 or 123 |
| 126 | exp animals/ |
| 127 | exp animal experimentation/ or exp animal experiment/ |
| 128 | exp models animal/ |
| 129 | nonhuman/ |
| 130 | exp vertebrate/ or exp vertebrates/ |
| 131 | or/126-130 |
| 132 | exp humans/ |
| 133 | exp human experimentation/ or exp human experiment/ |
| 134 | or/132-133 |

| MULTI-DATABASE STRATEGY: RESEARCH QUESTION 5 | |
|---|---|
| 135 | 131 not 134 |
| 136 | 124 not 135 |
| 137 | 125 and 136 |
| 138 | meta-analysis.pt. |
| 139 | meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ |
| 140 | ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf,kw. |
| 141 | ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf,kw. |
| 142 | ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf,kw. |
| 143 | (data synthes* or data extraction* or data abstraction*).ti,ab,kf,kw. |
| 144 | (handsearch* or hand search*).ti,ab,kf,kw. |
| 145 | (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf,kw. |
| 146 | (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf,kw. |
| 147 | (meta regression* or metaregression*).ti,ab,kf,kw. |
| 148 | (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw. |
| 149 | (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw. |
| 150 | (cochrane or (health adj2 technology assessment) or evidence report).jw. |
| 151 | (meta-analysis or systematic review).md. |
| 152 | (comparative adj3 (efficacy or effectiveness)).ti,ab,kf,kw. |
| 153 | (outcomes research or relative effectiveness).ti,ab,kf,kw. |
| 154 | ((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab,kf,kw. |
| 155 | or/138-154 |
| 156 | 136 and 155 |
| 157 | (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial).pt. |
| 158 | Randomized Controlled Trial/ |
| 159 | exp Randomized Controlled Trials as Topic/ |
| 160 | "Randomized Controlled Trial (topic)"/ |
| 161 | Controlled Clinical Trial/ |
| 162 | exp Controlled Clinical Trials as Topic/ |
| 163 | "Controlled Clinical Trial (topic)"/ |
| 164 | Randomization/ |
| 165 | Random Allocation/ |
| 166 | Double-Blind Method/ |
| 167 | Double Blind Procedure/ |
| 168 | Double-Blind Studies/ |
| 169 | Single-Blind Method/ |
| 170 | Single Blind Procedure/ |
| 171 | Single-Blind Studies/ |
| 172 | Placebos/ |
| 173 | Placebo/ |

| MULTI-DATABASE STRATEGY: RESEARCH QUESTION 5 | |
|---|---|
| 174 | Control Groups/ |
| 175 | Control Group/ |
| 176 | (random* or sham or placebo*).ti,ab,hw,kf,kw. |
| 177 | ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw. |
| 178 | ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw. |
| 179 | (control* adj3 (study or studies or trial*)).ti,ab,kf,kw. |
| 180 | (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw. |
| 181 | allocated.ti,ab,hw. |
| 182 | ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw. |
| 183 | or/157-182 |
| 184 | 136 and 183 |
| 185 | (disease adj2 (progress* or predict* or prognosis) adj2 (Outcome* or Risk* or Model*)).ti,ab,kf,kw. |
| 186 | (Predict* adj2 (Outcome* or Risk* or Model*)).ti,ab,kf,kw. |
| 187 | ((History or Variable* or Criteria or Scor* or Characteristic* or Finding* or Factor*) adj2 (Predict* or Model* or Decision* or Identif* or Prognos*)).ti,ab,kf,kf. |
| 188 | Decision*.ti,ab,kf,kw. and *Logistic Models/ |
| 189 | ((Prognostic or prognostic) adj2 (History or Variable* or Criteria or Scor* or Characteristic* or Finding* or Factor* or Model*)).ti,ab,kf,kw. |
| 190 | Disease model*.ti,ab,kf,kw. |
| 191 | 185 or 186 or 187 or 188 or 189 or 190 |
| 192 | 136 and 191 |
| 193 | Epidemiologic Methods/ |
| 194 | exp Epidemiologic Studies/ |
| 195 | Observational Studies as Topic/ |
| 196 | Clinical Studies as Topic/ |
| 197 | (Observational Study or Validation Studies or Clinical Study).pt. |
| 198 | (observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kf. |
| 199 | cohort*.ti,ab,kf. |
| 200 | (prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kf. |
| 201 | ((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,kf. |
| 202 | ((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data)).ti,ab,kf. |
| 203 | (retrospective adj7 (study or studies or design or analysis or analyses or data or review)).ti,ab,kf. |
| 204 | ((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,kf. |
| 205 | (case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,kf. |
| 206 | (population adj3 (study or studies or analysis or analyses)).ti,ab,kf. |
| 207 | (descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf. |
| 208 | ((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf. |
| 209 | (cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,kf. |
| 210 | ((natural adj experiment) or (natural adj experiments)).ti,ab,kf. |
| 211 | (quasi adj (experiment or experiments or experimental)).ti,ab,kf. |
| 212 | ((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or |

| MULTI-DATABASE STRATEGY: RESEARCH QUESTION 5 | |
|---|---|
| | design or analysis or analyses)).ti,ab,kf. |
| 213 | (prevalence adj3 (study or studies or analysis or analyses)).ti,ab,kf. |
| 214 | case series.ti,ab,kf. |
| 215 | case reports.pt. |
| 216 | (case adj3 (report or reports or study or studies or histories)).ti,ab,kf. |
| 217 | organizational case studies/ |
| 218 | or/193-217 |
| 219 | observational study/ |
| 220 | cohort analysis/ |
| 221 | longitudinal study/ |
| 222 | follow up/ |
| 223 | retrospective study/ |
| 224 | exp case control study/ |
| 225 | cross-sectional study/ |
| 226 | quasi experimental study/ |
| 227 | prospective study/ |
| 228 | (observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kw. |
| 229 | cohort*.ti,ab,kw. |
| 230 | (prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kw. |
| 231 | ((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,kw. |
| 232 | ((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data)).ti,ab,kw. |
| 233 | (retrospective adj7 (study or studies or design or analysis or analyses or data or review)).ti,ab,kw. |
| 234 | ((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,kw. |
| 235 | (case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,kw. |
| 236 | (population adj3 (study or studies or analysis or analyses)).ti,ab,kw. |
| 237 | (descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kw. |
| 238 | ((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kw. |
| 239 | (cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,kw. |
| 240 | ((natural adj experiment) or (natural adj experiments)).ti,ab,kw. |
| 241 | (quasi adj (experiment or experiments or experimental)).ti,ab,kw. |
| 242 | ((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,kw. |
| 243 | (prevalence adj3 (study or studies or analysis or analyses)).ti,ab,kw. |
| 244 | case series.ti,ab,kw. |
| 245 | case study/ |
| 246 | case report/ |
| 247 | (case adj3 (report or reports or study or studies or histories)).ti,ab,kw. |
| 248 | or/219-247 |
| 249 | 218 or 248 |
| 250 | 136 and 249 |

| MULTI-DATABASE STRATEGY: RESEARCH QUESTION 5 | |
|---|---|
| 251 | 137 or 156 or 184 or 192 or 250 |
| 252 | limit 251 to english language |
| 253 | limit 251 to french |
| 254 | 252 or 253 |
| 255 | remove duplicates from 254 |
| 256 | 255 not conference abstract.pt. |
| **Research Question 5: Antigen Tests** | |
| 1 | ((hepatitis C or hep C or hepC or HCV or hepacvirus or Hepacivirus) adj4 (antigen* or Ag or ABAG or AGAB) adj4 (diagnos* or detect* or test* or screen* or assay*)).ti,ab,kf,kw. |
| 2 | ((viral or virus) adj4 (antigen* or Ag) adj4 (diagnos* or detect* or test* or screen* or assay*)).ti,ab,kf,kw. |
| 3 | exp antigens/ |
| 4 | ((hepatitis C or hep C or hepC or HCV or hepacvirus or Hepacivirus) adj4 (diagnos* or detect* or test* or screen* or assay*)).ti,ab,kf,kw. |
| 5 | 3 and 4 |
| 6 | exp hepatitis c antigens/ |
| 7 | (diagnos* or detect* or test* or screen* or assay*).ti,ab,kf,kw. |
| 8 | 6 and 7 |
| 9 | 1 or 2 or 5 or 8 |
| 10 | ((hepatitis C or hep C or hepC or HCV or hepacvirus or Hepacivirus) adj4 core adj4 (diagnos* or detect* or test* or screen* or assay*)).ti,ab,kf,kw. |
| 11 | (HCV ag or HCVag or HCVcag or HCV c Ag or HCVc Ag or HCV cAg).ti,ab,kf,kw. |
| 12 | (Murex adj4 (Ag or antigen*)).ti,ab,kf,kw. |
| 13 | ((trak c or trackc) adj4 (diagnos* or detect* or test* or screen* or assay* or antigen* or Ag)).ti,ab,kf,kw. |
| 14 | (salck adj4 (ab or ag or antigen or antibody or abag or agab)).ti,ab,kf,kw. |
| 15 | 10 or 11 or 12 or 13 or 14 |
| 16 | 9 or 15 |
| 17 | Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/ or Hepatitis C Antibodies/ or exp Hepatitis C Antigens/ |
| 18 | (hepatitis C or hepC or hep C or hepacivirus* or HCV).ti,ab,kf,kw. |
| 19 | 17 or 18 |
| 20 | exp Mass screening/ |
| 21 | (detect or detection or screen or screens or screened or screening).ti,ab,kf,kw. |
| 22 | 20 or 21 |
| 23 | 19 and 22 |
| 24 | 16 and 23 |
| 25 | "sensitivity and specificity"/ or "limit of detection"/ or roc curve/ or diagnostic errors/ or false negative reactions/ or false positive reactions/ or "Predictive Value of Tests"/ |
| 26 | (Sensitivity or specificity).ti,ab,kf. |
| 27 | (false adj2 (positive* or negative*)).ti,ab,kf. |
| 28 | ((positive* or negative*) adj2 (predictive or likelihood)).ti,ab,kf. |
| 29 | (predictive valu* or validit*).ti,ab,kf. |
| 30 | (receiver adj2 operating).ti,ab. |
| 31 | (ROC or AUROC* or SROC or HSROC).ti,ab,kf. |
| 32 | ((under or over) adj2 curve).ti,ab,kf. |

| MULTI-DATABASE STRATEGY: RESEARCH QUESTION 5 | |
|---|---|
| 33 | (detect* adj2 (abilit* or rate*)).ti,ab,kf. |
| 34 | (Significant* adj2 (high or higher or low or lower or associate* or difference* or statistically or correlation*)).ti,ab,kf. |
| 35 | ((gold* or referen*) adj2 standard*).ti,ab,kf. |
| 36 | ((Evaluat* or compar*) adj2 (effica* or usefulness or useful or accura* or diagnostic)).ti,ab,kf. |
| 37 | 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 |
| 38 | 24 use ppez |
| 39 | 37 use ppez |
| 40 | ((hepatitis C or hep C or hepC or HCV or hepacvirus or Hepacivirus) adj4 (antigen* or Ag or ABAG or AGAB) adj4 (diagnos* or detect* or test* or screen* or assay*)).ti,ab,kw. |
| 41 | ((viral or virus) adj4 (antigen* or Ag) adj4 (diagnos* or detect* or test* or screen* or assay*)).ti,ab,kw. |
| 42 | exp antigen/ |
| 43 | ((hepatitis C or hep C or hepC or HCV or hepacvirus or Hepacivirus) adj4 (diagnos* or detect* or test* or screen* or assay*)).ti,ab,kw. |
| 44 | 42 and 43 |
| 45 | exp hepatitis c antigen/ |
| 46 | (diagnos* or detect* or test* or screen* or assay*).ti,ab,kw. |
| 47 | 45 and 46 |
| 48 | exp antigen detection/ |
| 49 | (hepatitis C or hep C or hepC or HCV or hepacvirus or Hepacivirus).ti,ab,kw. |
| 50 | 48 and 49 |
| 51 | 40 or 41 or 44 or 47 or 50 |
| 52 | ((hepatitis C or hep C or hepC or HCV or hepacvirus or Hepacivirus) adj4 core adj4 (diagnos* or detect* or test* or screen* or assay*)).ti,ab,kw. |
| 53 | (HCV ag or HCVag or HCVcag or HCV c Ag or HCVc Ag or HCV cAg).ti,ab,kw. |
| 54 | (Murex adj4 (Ag or antigen*)).ti,ab,kw. |
| 55 | ((trak c or trackc) adj4 (diagnos* or detect* or test* or screen* or assay* or antigen* or Ag)).ti,ab,kw. |
| 56 | (salck adj4 (ab or ag or antigen or antibody or abag or agab)).ti,ab,kw. |
| 57 | 52 or 53 or 54 or 55 or 56 |
| 58 | 51 or 57 |
| 59 | exp hepatitis C/ or exp Hepatitis C virus/ or exp hepatitis C antibody/ or exp hepatitis C antigen/ |
| 60 | (hepatitis C or hepC or hep C or hepacivirus* or HCV).ti,ab,kw. |
| 61 | 59 or 60 |
| 62 | exp antibody screening/ or exp mass screening/ or exp screening/ or exp screening test/ |
| 63 | (detect or detection or screen or screens or screened or screening).ti,ab,kw. |
| 64 | 62 or 63 |
| 65 | 61 and 64 |
| 66 | 58 and 65 |
| 67 | diagnostic accuracy/ or "sensitivity and specificity"/ or "limit of detection"/ or receiver operating characteristic/ or exp diagnostic error/ or predictive value/ or diagnostic value/ or Diagnostic test accuracy study/ |
| 68 | (Sensitivity or specificity).ti,ab,kw. |
| 69 | (false adj2 (positive* or negative*)).ti,ab,kw. |
| 70 | (predictive valu* or validit*).ti,ab,kw. |

| MULTI-DATABASE STRATEGY: RESEARCH QUESTION 5 | |
|---|---|
| 71 | ((test or tests or testing or tested or diagnostic* or diagnosis) adj2 (performance or accura* or value)).ti,ab,kw. |
| 72 | (receiver adj2 operating).ti,ab,kw. |
| 73 | (ROC or AUROC* or SROC or HSROC).ti,ab,kw. |
| 74 | ((under or over) adj2 curve*).ti,ab,kw. |
| 75 | (detect* adj2 (abilit* or rate*)).ti,ab,kw. |
| 76 | (Significant* adj2 (high or higher or low or lower or associate* or difference* or statistically or correlation*)).ti,ab,kw. |
| 77 | ((gold or reference) adj2 standard*).ti,ab,kw. |
| 78 | ((Evaluat* or compar*) adj2 (effica* or usefulness or useful or accurac* or diagnostic)).ti,ab,kw. |
| 79 | 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 |
| 80 | 66 use oemezd |
| 81 | 79 use oemezd |
| 82 | 38 or 80 |
| 83 | meta-analysis.pt. |
| 84 | meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ |
| 85 | ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf,kw. |
| 86 | ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf,kw. |
| 87 | ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf,kw. |
| 88 | (data synthes* or data extraction* or data abstraction*).ti,ab,kf,kw. |
| 89 | (handsearch* or hand search*).ti,ab,kf,kw. |
| 90 | (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf,kw. |
| 91 | (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf,kw. |
| 92 | (meta regression* or metaregression*).ti,ab,kf,kw. |
| 93 | (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw. |
| 94 | (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw. |
| 95 | (cochrane or (health adj2 technology assessment) or evidence report).jw. |
| 96 | (meta-analysis or systematic review).md. |
| 97 | (comparative adj3 (efficacy or effectiveness)).ti,ab,kf,kw. |
| 98 | (outcomes research or relative effectiveness).ti,ab,kf,kw. |
| 99 | ((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab,kf,kw. |
| 100 | or/83-99 |
| 101 | (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial).pt. |
| 102 | Randomized Controlled Trial/ |
| 103 | exp Randomized Controlled Trials as Topic/ |
| 104 | "Randomized Controlled Trial (topic)"/ |
| 105 | Controlled Clinical Trial/ |
| 106 | exp Controlled Clinical Trials as Topic/ |
| 107 | "Controlled Clinical Trial (topic)"/ |
| 108 | Randomization/ |

| MULTI-DATABASE STRATEGY: RESEARCH QUESTION 5 | |
|---|---|
| 109 | Random Allocation/ |
| 110 | Double-Blind Method/ |
| 111 | Double Blind Procedure/ |
| 112 | Double-Blind Studies/ |
| 113 | Single-Blind Method/ |
| 114 | Single Blind Procedure/ |
| 115 | Single-Blind Studies/ |
| 116 | Placebos/ |
| 117 | Placebo/ |
| 118 | Control Groups/ |
| 119 | Control Group/ |
| 120 | (random* or sham or placebo*).ti,ab,hw,kf,kw. |
| 121 | ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw. |
| 122 | ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw. |
| 123 | (control* adj3 (study or studies or trial*)).ti,ab,kf,kw. |
| 124 | (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw. |
| 125 | allocated.ti,ab,hw. |
| 126 | ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw. |
| 127 | or/101-126 |
| 128 | Epidemiologic Methods/ |
| 129 | exp Epidemiologic Studies/ |
| 130 | Observational Studies as Topic/ |
| 131 | Clinical Studies as Topic/ |
| 132 | (Observational Study or Validation Studies or Clinical Study).pt. |
| 133 | (observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kf. |
| 134 | cohort*.ti,ab,kf. |
| 135 | (prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kf. |
| 136 | ((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,kf. |
| 137 | ((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data)).ti,ab,kf. |
| 138 | (retrospective adj7 (study or studies or design or analysis or analyses or data or review)).ti,ab,kf. |
| 139 | ((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,kf. |
| 140 | (case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,kf. |
| 141 | (population adj3 (study or studies or analysis or analyses)).ti,ab,kf. |
| 142 | (descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf. |
| 143 | ((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf. |
| 144 | (cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,kf. |
| 145 | ((natural adj experiment) or (natural adj experiments)).ti,ab,kf. |
| 146 | (quasi adj (experiment or experiments or experimental)).ti,ab,kf. |
| 147 | ((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf. |

| MULTI-DATABASE STRATEGY: RESEARCH QUESTION 5 | |
|---|---|
| 148 | (prevalence adj3 (study or studies or analysis or analyses)).ti,ab,kf. |
| 149 | case series.ti,ab,kf. |
| 150 | case reports.pt. |
| 151 | (case adj3 (report or reports or study or studies or histories)).ti,ab,kf. |
| 152 | organizational case studies/ |
| 153 | or/128-152 |
| 154 | observational study/ |
| 155 | cohort analysis/ |
| 156 | longitudinal study/ |
| 157 | follow up/ |
| 158 | retrospective study/ |
| 159 | exp case control study/ |
| 160 | cross-sectional study/ |
| 161 | quasi experimental study/ |
| 162 | prospective study/ |
| 163 | (observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kw. |
| 164 | cohort*.ti,ab,kw. |
| 165 | (prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kw. |
| 166 | ((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,kw. |
| 167 | ((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data)).ti,ab,kw. |
| 168 | (retrospective adj7 (study or studies or design or analysis or analyses or data or review)).ti,ab,kw. |
| 169 | ((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,kw. |
| 170 | (case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,kw. |
| 171 | (population adj3 (study or studies or analysis or analyses)).ti,ab,kw. |
| 172 | (descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kw. |
| 173 | ((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kw. |
| 174 | (cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,kw. |
| 175 | ((natural adj experiment) or (natural adj experiments)).ti,ab,kw. |
| 176 | (quasi adj (experiment or experiments or experimental)).ti,ab,kw. |
| 177 | ((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,kw. |
| 178 | (prevalence adj3 (study or studies or analysis or analyses)).ti,ab,kw. |
| 179 | case series.ti,ab,kw. |
| 180 | case study/ |
| 181 | case report/ |
| 182 | (case adj3 (report or reports or study or studies or histories)).ti,ab,kw. |
| 183 | or/154-182 |
| 184 | 153 or 183 |
| 185 | (disease adj2 (progress* or predict* or prognosis) adj2 (Outcome* or Risk* or Model*)).ti,ab,kf,kw. |
| 186 | (Predict* adj2 (Outcome* or Risk* or Model*)).ti,ab,kf,kw. |

| MULTI-DATABASE STRATEGY: RESEARCH QUESTION 5 | |
|---|---|
| 187 | ((History or Variable* or Criteria or Scor* or Characteristic* or Finding* or Factor*) adj2 (Predict* or Model* or Decision* or Identif* or Prognos*)).ti,ab,kf,kf. |
| 188 | Decision*.ti,ab,kf,kw. and *Logistic Models/ |
| 189 | ((Prognostic or prognostic) adj2 (History or Variable* or Criteria or Scor* or Characteristic* or Finding* or Factor* or Model*)).ti,ab,kf,kw. |
| 190 | Disease model*.ti,ab,kf,kw. |
| 191 | 185 or 186 or 187 or 188 or 189 or 190 |
| 192 | 39 or 79 |
| 193 | 82 and 100 |
| 194 | 82 and 127 |
| 195 | 82 and 184 |
| 196 | 82 and 191 |
| 197 | 82 and 192 |
| 198 | 193 or 194 or 195 or 196 or 197 |
| 199 | exp animals/ |
| 200 | exp animal experimentation/ or exp animal experiment/ |
| 201 | exp models animal/ |
| 202 | nonhuman/ |
| 203 | exp vertebrate/ or exp vertebrates/ |
| 204 | or/199-203 |
| 205 | exp humans/ |
| 206 | exp human experimentation/ or exp human experiment/ |
| 207 | or/205-206 |
| 208 | 204 not 207 |
| 209 | 198 not 208 |
| 210 | limit 209 to english language |
| 211 | limit 209 to french |
| 212 | 210 or 211 |
| 213 | 212 not conference abstract.pt. |
| 214 | remove duplicates from 213 |

| OTHER DATABASES | |
|---|---|
| PubMed | A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used. |

CADTH

# Appendix 2: Full-Text Screening Checklist

Reviewer: _____ Date: _____

| **Ref ID:**_____ **Author:** _____ **Publication Year:** _____ | | | |
|---|---|---|---|
| **Did the study include:** | **Yes (Include)** | **Unclear (Include)[a]** | **No (Exclude)** |
| 1) Non-pregnant, treatment-naive adults with unknown liver enzyme values? | ☐ | ☐ | ☐ |
| 2) Q1 to Q4: Any screening program for HCV infection?<br>Q5 (clinical validity): Ab or Ag test? | ☐ | ☐ | ☐ |
| 3) Q1 to Q4: A comparison with no screening?<br>Q5 (clinical validity): PCR diagnostic test? | ☐ | ☐ | ☐ |
| 4) Any of the following as the study outcomes?<br>**Q1 (clinical effectiveness)**<br>• Mortality due to HCV infection<br>• Morbidity due to HCV infection (e.g., cirrhosis [compensated or decompensated] and HCC)<br>• Rate of liver transplantation<br>• Quality of life<br>• Reduced HCV transmission<br>• Sustained or improved virologic response<br>• Behavioural changes to improve health outcomes<br>• Histological improvements.<br>**Q2 (harms)**<br>• Over-diagnosis<br>• Over-treatment<br>• False-positives<br>• False-negatives<br>• Harms of follow-up tests (including biopsy)<br>• Insurance premiums<br>• Labelling<br>• Abuse or violence<br>• Anxiety<br>• Partner discord<br>**Q3 (cost-effectiveness)**<br>• CEA outcomes (e.g., ICER, ICUR, CBR)<br>• Budget impact analysis outcomes<br>**Q4 (patients' preferences)**<br>Patients' preferences and values regarding HCV screening; for example:<br>• Willingness to be screened<br>• Factors considered in decisions to be screened | ☐ | ☐ | ☐ |

| **Ref ID:**_____ **Author:** _____ **Publication Year:** _____ | | | |
|---|---|---|---|
| **Did the study include:** | **Yes (Include)** | **Unclear (Include)[a]** | **No (Exclude)** |
| **Q5 (clinical validity)**<br>• Ab+RNA+<br>• Ab–RNA+<br>• Ab+RNA–<br>• Ab–RNA– | | | |
| 5) Any of the following study designs?<br><br>**Q1 (clinical effectiveness), Q2 (harms)**<br>• RCT<br>• Non-randomized study with a comparator group<br>• Non-randomized study without a comparator group<br>• Disease-progression modelling study<br>**Q3 (cost-effectiveness)**<br>• RCT<br>• Economic evaluation<br>• Modelling study<br>**Q4 (patients' preferences)**<br>• Qualitative study<br>• Survey<br>• Mixed-methods study<br>**Q5 (clinical validity)**<br>• Cross-sectional study | ☐ | ☐ | ☐ |
| 6) Conducted in a primary care setting, setting generalizable to primary care, or other setting in which screening is commonly performed (e.g., emergency department, urgent care unit)? | ☐ | ☐ | ☐ |
| 7) Conducted in the following country settings?<br><br>**Q3 (cost-effectiveness)**<br>• Canada<br>**Q5 (clinical validity)**<br>• Low-to-moderate HCV prevalence country | ☐ | ☐ | ☐ |
| 8) Published in English or French? | ☐ | ☐ | ☐ |
| **Decision to include the study in the review:** | **Yes**☐ | | **No**☐ |
| **Reason(s) for exclusion:** | ☐ Inappropriate study population<br>☐ No intervention of interest<br>☐ No/inappropriate comparator[b]<br>☐ No relevant outcomes<br>☐ Irrelevant study type<br>☐ Irrelevant language of publication<br>☐ Not primary report of study<br>☐ Study description only<br>☐ Other: | | |

Ab = antibody; Ag = antigen; CBR = cost-benefit ratio; CEA = cost-effectiveness analysis; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; ID = identification; PCR = polymerase chain reaction; Q = question; RCT = randomized controlled trial; RNA = ribonucleic acid.
Note: If all items are answered "yes" or "unclear," then the study is included.
[a] Discuss with a second reviewer.
[b] Diagnostic test (PCR) for Q5.

# Appendix 3: Data Extraction Forms — Harms, Cost-Effectiveness, Patient Preferences, and Clinical Validity of Screening With Ab and Ag Tests

| DATA EXTRACTION FORM: Frequency of Harms (Q2) | |
|---|---|
| Author | |
| Year of publication | |
| Country | |
| RefID | |
| Study design | |
| Care setting | |
| Type of analysis | |
| Analysis perspective | |
| Description of study population | e.g., HCV high-risk group |
| Number enrolled | |
| Number completing study | |
| Patients eligible/included only if asymptomatic (Y/N/NR) | |
| If **symptomatic** patients included, n (%) of population | |
| Patients eligible/included only if non-pregnant (Y/N/NR) | |
| If **pregnant** patients included, n (%) of population | |
| Patients eligible/included only if treatment-naive (Y/N/NR) | |
| If **treated** patients were included, n (%) of population | |
| Patients eligible/included only if at least 18 years old (Y/N/NR) | |
| If **patients under 18** were included, n (%) of population | |
| Patients eligible/included if liver enzymes unknown (Y/N/NR) | |
| If patients with **known liver enzymes** were included, n (%) of population | |
| Other selection criteria | |
| Age of Patients Completing Study | |
| Female, n (%) | |
| Male, n (%) | |
| Other | |
| Description of intervention | |
| Description of comparator (if applicable) | |
| Conflicts of interest | |
| Financial sponsorship | e.g., funding, honorariums, consultancies, employment |
| Other support | e.g., in-kind |

| RESULTS | |
|---|---|
| Author (date) [refID] | |
| Group | |
| Over-diagnosis | |
| Over-treatment | |
| False positives | |
| False negatives | |
| Harms of follow-up tests (including biopsy) | |
| Labelling | |
| Abuse or violence | |
| Anxiety | |
| Partner discord | |
| Comments | |

Ab = antibody; Ag = antigen; HCV = hepatitis C virus; N = No; NR = not reported; refID = reference identification; Y = Yes.

| DATA EXTRACTION FORM: Cost-Effectiveness (Q3) | |
|---|---|
| Author | |
| Year of publication | |
| Country | |
| RefID | |
| Study design | |
| Care setting | |
| Type of analysis | |
| Analysis perspective | |
| Description of study population | e.g., HCV high-risk group |
| Number enrolled | |
| Number completing study | |
| Patients eligible/included only if asymptomatic (Y/N/NR) | |
| If **symptomatic** patients included, n (%) of population | |
| Patients eligible/included only if non-pregnant (Y/N/NR) | |
| If **pregnant** patients included, n (%) of population | |
| Patients eligible/included only if treatment-naive (Y/N/NR) | |
| If **treated** patients were included, n (%) of population | |
| Patients eligible/included only if at least 18 years old (Y/N/NR) | |
| If **patients under 18** were included, n (%) of population | |
| Patients eligible/included if liver enzymes unknown (Y/N/NR) | |
| If patients with **known liver enzymes** were included, n (%) of population | |
| Other selection criteria | |
| Age of patients completing study | |
| Female, n (%) | |
| Male, n (%) | |
| Other | |
| Description of intervention | |
| Description of comparator | |
| Time horizon | |
| Model Inputs | |
| Sources of utilities | |
| Main assumptions | |
| Planned sensitivity analyses | |
| Conflicts of interest | |
| Financial sponsorship | e.g., funding, honorariums, consultancies, employment |
| Other support | e.g., in-kind |

| RESULTS | |
|---|---|
| Author (date) [ref ID] | |
| Group | |
| ICER ($/QALY) | |
| ICUR | |
| Cost-benefit ratio | |
| Budget impact analyses | |
| Comments | |

HCV = hepatitis C virus; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; n = number; N = no; NR = not reported; Q = question; QALY = quality-adjusted life-year; refID = reference identification; Y = yes.

| DATA ABSTRACTION FORM: Patient Preferences (Q4)[a] | |
|---|---|
| Author | |
| Year of publication | |
| Country where data generated | |
| Funding sources | |
| Ethics approval | ☐ Yes<br>☐ No<br><br>Comments: |
| Study design | ☐ Descriptive survey<br>☐ Ethnography<br>☐ Phenomenology<br>☐ Grounded theory<br>☐ Qualitative description<br>☐ Other (specify): |
| Study objectives | |
| Description of study setting | |
| Description of screening | |
| Inclusion and exclusion criteria | |
| Recruitment method | |
| Sample size | |
| Population type | e.g., PWID, general population, incarcerated individuals |
| Sex (% male and female) | |
| Age | |
| % of participants with previous HCV testing | |
| Race | |
| Education | |
| Income and/or employment status | |
| Relationshipstatus | |
| Other HCV risk factors | |
| Other factors that may be associated with HCV testing | e.g., having a primary health care provider, area of residence |
| Data collection methods | ☐ Questionnaire<br>☐ Interview<br>☐ Focus group<br>☐ Observation<br>☐ Document review<br>☐ Other (specify): |
| Description of type of interview, if applicable | ☐ Unstructured<br>☐ Semi-structured<br>☐ Structured |
| Interview delivery, if applicable | ☐ In-person<br>☐ Telephone<br>☐ Unclear |
| Data analysis methods | |

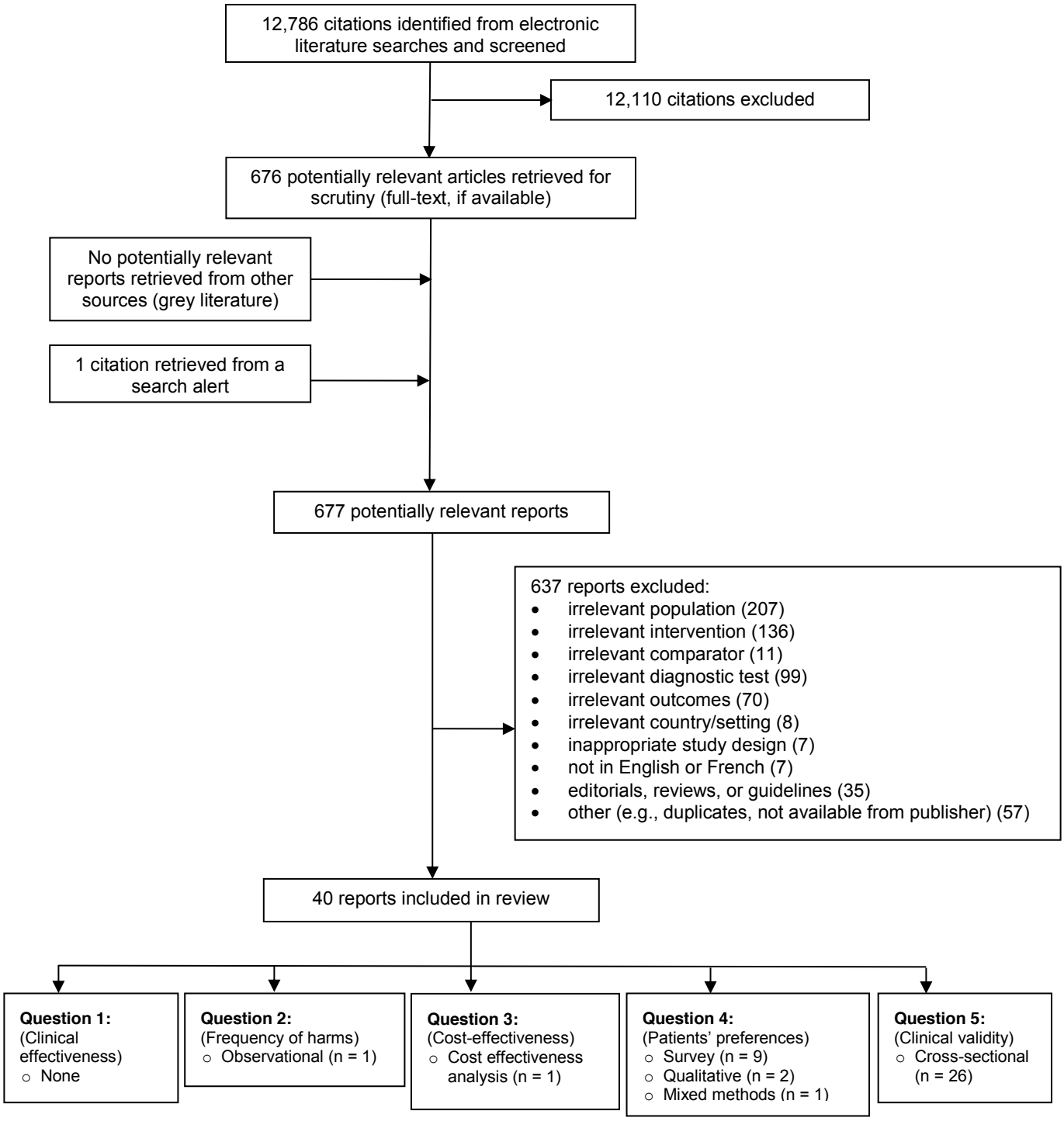
HCV = hepatitis C virus; PWID = people who inject drugs; Q = question.
[a] Study and participant characteristics were extracted using this form. Verbatim results statements were captured directly from PDF versions of the included study publications using NVivo software; as such, no data extraction form for results statements was used.

| DATA EXTRACTION FORM: Clinical Validity of General Population Screening With Ab and Ag Tests (Q5) | |
|---|---|
| Author, year of publication, refID | |
| Country | |
| Study design | |
| Study dates or duration | |
| Care setting or source of patients | |
| Recruitment strategy | |
| Description of study population | |
| Number of patients eligible | |
| Number of included patients | |
| Patients eligible/included only if asymptomatic (Y/N/NR) | |
| If **symptomatic** patients included, n (%) of population | |
| Patients eligible/included only if non-pregnant (Y/N/NR) | |
| If **pregnant** patients included, n (%) of population | |
| Patients eligible/included only if at least 18 years old (Y/N/NR) | |
| If **patients under 18** were included, n (%) of population | |
| Patients eligible/included if liver enzymes unknown or normal (Y/N/NR) | |
| If patients with **abnormal liver enzymes** were included, n (%) of population | |
| Age of patients completing study | |
| Female, n (%) | |
| Male, n (%) | |
| Other | |
| First Ab or Ag test | |
| Comments about Ab or Ag test | e.g., threshold |
| Supplemental or confirmation tests | |
| Comments about supplemental or confirmation tests | |
| Second Ab or Ag test (if applicable) | |
| Comments about second Ab or Ag test | |
| PCR test | |
| Comments about PCR test | e.g., threshold |
| Timing or interval between Ab or Ag test and PCR test | |
| Conflicts of interest | |
| Financial sponsorship | e.g., funding, honorariums, consultancies, employment |
| Other support | e.g., in-kind |
| Other comments | |

| RESULTS | | | |
|---|---|---|---|
| Author, year of publication, refID | | | |
| Name of Ab or Ag test | Name of PCR test | | |
| | **RNA+** | **RNA–** | **Total** |
| **Ab+ (or Ag+)** | | | |
| **Ab– (or Ag–)** | | | |
| **Total** | | | |
| Definition of Ab+ (or Ag+) | | | |
| Defintion of Ab– (or Ag–) | | | |
| Definition of RNA+ | | | |
| Definition of RNA– | | | |
| Other comments | | | |

Ab = antibody; Ag = antigen; N = no; NR = not reported; Q = question; PCR = polymerase chain reaction; refID = reference identification; RNA = ribonucleic acid; refID = reference identification; Y = yes.

# Appendix 4: Study Selection (PRISMA) Flow Chart



# Appendix 5: List of Excluded Studies

## Table 5: List of Studies Excluded From the Systematic Review — November 2015 Database Search

| Study | Reason for Exclusion |
|---|---|
| Summaries for patients: Screening for liver cancer in patients with hepatitis C virus infection and cirrhosis. Ann Intern Med. 2011;154(2):I-36. | Other |
| Should you be tested for hepatitis C? New treatments promise high cure rates with fewer side effects. But carefully consider the pros and cons of testing. Harv Mens Health Watch. 2012 Sep;17(2):6, 2012. | Editorial or review |
| Guidelines for the screening, care and treatment of persons with hepatitis C infection. Geneva: World Health Organization; 2014 Apr. | Guideline |
| Aamado L, Villar LM, Paula VS, Almeida AJ, Gaspar AMC. Detection of hepatitis A, B, and C virus-specific antibodies using oral fluid for epidemiological studies. Memorias do Instituto Oswaldo Cruz. 2006;101(2):149-55. | Reference standard |
| Abdel-Hamid M, El-Daly M, El-Kafrawy S, Mikhail N, Strickland GT, Fix AD. Comparison of second- and third-generation enzyme immunoassays for detecting antibodies to hepatitis C virus. J Clin Microbiol. 2002 May;40(5):1656-9. | Population |
| Agarwal N, Chatterjee K, Coshic P, Borgohain M. Nucleic acid testing for blood banks: an experience from a tertiary care centre in New Delhi, India. Transfus Apheresis Sci. 2013 Dec;49(3):482-4. | Intervention |
| Agha S, Tanaka Y, Saudy N, Kurbanov F, Abo-Zeid M, El-Malky M, et al. Reliability of hepatitis C virus core antigen assay for detection of viremia in HCV genotypes 1, 2, 3, and 4 infected blood donors: a collaborative study between Japan, Egypt, and Uzbekistan. J Med Virol. 2004 Jun;73(2):216-22. | Intervention |
| Albertoni G, Arnoni CP, Araujo PR, Carvalho FO, Barreto JA. Signal to cut-off (S/CO) ratio and detection of HCV genotype 1 by real-time PCR one-step method: is there any direct relationship? Braz J Infect Dis. 2010 Mar;14(2):147-52. | Outcomes |
| Ali A, Lal A. False positivity of serological tests for hepatitis C virus. J Ayub Med Coll Abbottabad. 2010 Apr;22(2):43-5. | Population |
| Anderson EM, Mandeville RP, Hutchinson SJ, Cameron SO, Mills PR, Fox R, et al. Evaluation of a general practice based hepatitis C virus screening intervention. Scott Med J. 2009 Aug;54(3):3-7. | Outcomes |
| Ansaldi F, Bruzzone B, Testino G, Bassetti M, Gasparini R, Crovari P, et al. Combination hepatitis C virus antigen and antibody immunoassay as a new tool for early diagnosis of infection. J Viral Hepat. 2006 Jan;13(1):5-10. | Population |
| Aoyagi K, Iida K, Ohue C, Matsunaga Y, Tanaka E, Kiyosawa K, et al. Performance of a conventional enzyme immunoassay for hepatitis C virus core antigen in the early phases of hepatitis C infection. Clin Lab. 2001;47(3-4):119-27. | Intervention |
| Aparicio T, Bonnaud G, Lucet JC, Vuagnat A, Leroy C, Bouchaud O, et al. Evaluation of three testing strategies for detection of hepatitis C in a hospital medical consultation and in an HIV testing center. Gastroenterol Clin Biol. 2001;25(5):515-20. | Outcomes |
| Arduino JM, Stuver SO, Spiegelman D, Okayama A, Tabor E, Yu MW, et al. Assessment of markers of hepatitis C virus infection in a Japanese adult population. J Infect Dis. 2001;184(10):1229-35. | Intervention |
| Arrada A, Zbar OZD, Vasseur V. Prevalence of HBV and HCV infections and incidence of HCV infection after 3, 6 and 12 months detention in La Sante prison, Paris. Ann Med Interne (Paris). 2001;152(7 Suppl):2S6-8. | Population |
| Aspinall EJ, Doyle JS, Corson S, Hellard ME, Hunt D, Goldberg D, et al. Targeted hepatitis C antibody testing interventions: a systematic review and meta-analysis. Eur J Epidemiol. 2015 Feb;30(2):115-29. | Editorial or review |

## Table 5: List of Studies Excluded From the Systematic Review — November 2015 Database Search

| Study | Reason for Exclusion |
|---|---|
| Asrani SK, Davis GL. Impact of birth cohort screening for hepatitis C. Curr Gastroenterol Rep. 2014 Apr;16(4):381, 2014. | Editorial or review |
| Attallah AM, Ismail H, Tabll AA, Shiha GE, El-Dosoky I. A novel antigen detection immunoassay for field diagnosis of hepatitis C virus infection. J Immunoassay Immunochem. 2003;24(4):395-407. | Population |
| Attallah AM, Omran MM, Nasif WA, Ghaly MF, El-Shanshoury A, Abdalla MS, et al. Diagnostic performances of hepatitis C virus-NS4 antigen in patients with different liver pathologies. Arch Med Res. 2012 Oct;43(7):555-62. | Population |
| Bamaga MS, Bokhari FF, Aboud AM, Al-Malki M, Alenzi FQ. Nucleic acid amplification technology screening for hepatitis C virus and human immunodeficiency virus for blood donations. Saudi Med J. 2006;27(6):781-7. | Intervention |
| Bassit L, Van Heuverswyn H, De Bosschere K, Nishiya A, Carrilho FJ, Moraes C, et al. Comparative study of two anti-HCV screening tests in a large genotyped population of Brazilian dialysis patients. European Journal of Clinical Microbiology and Infectious Diseases. 2002;21(5):404-6. | Population |
| Beltran M, Navas MC, De la Hoz F, Mercedes MM, Jaramillo S, Estrada C, et al. Hepatitis C virus seroprevalence in multi-transfused patients in Colombia. J Clin Virol. 2005 Dec;34 Suppl 2:S33-8. | Population |
| Benouda A, Boujdiya Z, Ahid S, Abouqal R, Adnaoui M. Prevalence of hepatitis C virus infection in Morocco and serological tests assessment of detection for the viremia prediction. Pathol Biol (Paris). 2009 Jul;57(5):368-72. | Intervention |
| Blanchet E, Defossez G, Verneau A, Ingrand I, Silvain C, Beauchant M, et al. Epidemiology and management of care of hepatitis C infection in the Poitou-Charentes region in 1997 and 2000. Gastroenterol Clin Biol. 2003 Nov;27(11):1026-30. | Intervention |
| Bradshaw CS, Pierce LI, Tabrizi SN, Fairley CK, Garland SM. Screening injecting drug users for sexually transmitted infections and blood borne viruses using street outreach and self collected sampling. Sex Transm Infect. 2005 Feb;81(1):53-8. | Outcomes |
| Brett-Major DM, Frick KD, Malia JA, Hakre S, Okulicz JF, Beckett CG, et al. Costs and consequences: Hepatitis C seroprevalance in the military and its impact on potential screening strategies. Hepatology. 2015 Oct 20. | Reference standard |
| Brouard C, Le Strat Y, Larsen C, Jauffret-Roustide M, Lot F, Pillonel J. The undiagnosed chronically-infected HCV population in France. Implications for expanded testing recommendations in 2014. PLoS ONE. 2015;10(5):e0126920. | Intervention |
| Bruhn R, Lelie N, Busch M, Kleinman S, International NAT Study Group. Relative efficacy of nucleic acid amplification testing and serologic screening in preventing hepatitis C virus transmission risk in seven international regions. Transfusion. 2015 Jun;55(6):1195-205. | Outcomes |
| Bruneau J, Zang G, Abrahamowicz M, Jutras-Aswad D, Daniel M, Roy E. Sustained drug use changes after hepatitis C screening and counseling among recently infected persons who inject drugs: a longitudinal study. Clin Infect Dis. 2014 Mar;58(6):755-61. | Comparator |
| Busch MP, Watanabe KK, Smith JW, Hermansen SW, Thomson RA. False-negative testing errors in routine viral marker screening of blood donors. For the Retrovirus Epidemiology Donor Study. Transfusion. 2000 May;40(5):585-9. | Study design |
| Caballeria L, Pera G, Bernad J, Canut S, Navarro E, Bruguera M. Strategies for the detection of hepatitis C viral infection in the general population. Rev Clin Esp (Barc). 2014 Jun;214(5):242-6. | Outcomes |
| Cadranel JF, Di Martino V, Cesbron H, Cazier A, Demontis R, Coutarel P, et al. Hepatitis C epidemiology at a general hospital center. Management and natural history as a function of the manner of identification. Gastroenterol Clin Biol. 2000 Feb;24(2):161-7. | Comparator |

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| Study | Reason for Exclusion |
|---|---|
| Calderon Y, Cowan E, Schramm C, Stern S, Brusalis C, Iscoe M, et al. HCV and HBV testing acceptability and knowledge among urban emergency department patients and pharmacy clients. Prev Med. 2014 Apr;61:29-33. | Intervention |
| Campos-Outcalt D. Hepatitis C: New CDC screening recommendations. J Fam Pract. 2012;61(12):744-6. | Editorial or review |
| Cano H, Candela MJ, Lozano ML, Vicente V. Application of a new enzyme-linked immunosorbent assay for detection of total hepatitis C virus core antigen in blood donors. Transfus Med. 2003 Oct;13(5):259-66. | Intervention |
| Cao J, Chen Q, Zhang H, Qi P, Liu C, Yang X, et al. Novel evolved immunoglobulin (ig)-binding molecules enhance the detection of igm against hepatitis c virus. PLoS ONE. 2011;6(4). | Reference standard |
| Centers for Disease Control and Prevention (CDC). Locations and reasons for initial testing for hepatitis C infection--chronic hepatitis cohort study, United States, 2006-2010. MMWR Morb Mortal Wkly Rep. 2013 Aug 16;62(32):645-8. | Population |
| Chakravarti A, Chauhan MS, Dogra G, Banerjee S. Hepatitis C virus core antigen assay: Can we think beyond convention in resource limited settings? Braz J Infect Dis. 2013;17(3):369-74. | Population |
| Chen JY, Wang JH, Lin CY, Chen PF, Tseng PL, Chen CH, et al. Lower prevalence of hypercholesterolemia and hyperglyceridemia found in subjects with seropositivity for both Hepatitis B and C strains independently. Journal of Gastroenterology and Hepatology (Australia). 2010;25(11):1763-8. | Outcomes |
| Chiquete E, Sanchez LV, Becerra G, Quintero A, Maldonado M, Panduro A. Performance of the serologic and molecular screening of blood donations for the hepatitis B and C viruses in a Mexican Transfusion Center. Ann Hepatol. 2005 Oct;4(4):275-8. | Study design |
| Chou R, Clark EC, Helfand M,.Preventive Services. Screening for hepatitis C virus infection: a review of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2004 Mar 16;140(6):465-79. | Editorial or review |
| Chou R, Cottrell EB, Wasson N, Rahman B, Guise JM. Screening for hepatitis C virus infection in adults: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2013 Jan 15;158(2):101-8. | Editorial or review |
| Cipriano LE, Zaric GS, Holodniy M, Bendavid E, Owens DK, Brandeau ML. Cost Effectiveness of Screening Strategies for Early Identification of HIV and HCV Infection in Injection Drug Users. PLoS ONE. 2012;7(9). | Population |
| Colin C, Lanoir D, Touzet S, Meyaud-Kraemer L, Bailly F, Trepo C, et al. Sensitivity and specificity of third-generation hepatitis C virus antibody detection assays: an analysis of the literature. J Viral Hepat. 2001 Mar;8(2):87-95. | Editorial or review |
| Contreras AM, Tornero-Romo CM, Toribio JG, Celis A, Orozco-Hernandez A, Rivera PK, et al. Very low hepatitis C antibody levels predict false-positive results and avoid supplemental testing. Transfusion. 2008;48(12):2540-8. | Population |
| Cox J, Graves L, Marks E, Tremblay C, Stephenson R, Lambert-Lanning A, et al. Knowledge, attitudes and behaviours associated with the provision of hepatitis C care by Canadian family physicians. J Viral Hepat. 2011;18(7):e332-e340. | Intervention |
| Craine N, Walker M, Carnwath T, Klee H. Hepatitis C testing and injecting risk behaviour: The results of a UK based pilot study. International Journal of Drug Policy. 2004;15(2):115-22. | Outcomes |
| Cramp ME, Rosenberg WM, Ryder SD, Blach S, Parkes J. Modelling the impact of improving screening and treatment of chronic hepatitis C virus infection on future hepatocellular carcinoma rates and liver-related mortality. BMC Gastroenterology. 2014;14(1). | Population |
| Dawar M, Stuart TL, Sweet LE, Neatby AM, Abbott LP, Andonov AP, et al. Canadian hepatitis C look-back investigation to detect transmission from an infected general surgeon. Canadian | Intervention |

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| Study | Reason for Exclusion |
|---|---|
| Journal of Infectious Diseases and Medical Microbiology. 2010;21(1):e6-e11. | |
| De Almeida Ponde RA. Enzyme-linked immunosorbent/chemiluminescence assays, recombinant immunoblot assays and nucleic acid tests in the diagnosis of HCV infection. European Journal of Clinical Microbiology and Infectious Diseases. 2013;32(8):985-8. | Editorial or review |
| Defossez G, Verneau A, Ingrand I, Silvain C, Ingrand P, Beauchant M, et al. Evaluation of the French national plan to promote screening and early management of viral hepatitis C, between 1997 and 2003: a comparative cross-sectional study in Poitou-Charentes region. Eur J Gastroenterol Hepatol. 2008 May;20(5):367-72. | Intervention |
| Delage G, Myhal G, Gregoire Y, Simmons-Coley GM. Donors' psychological reactions to deferral following false-positive screening test results. Vox Sang. 2014 Aug;107(2):132-9. | Intervention |
| Delarocque-Astagneau E, Meffre C, Dubois F, Pioche C, Le Strat Y, Roudot-Thoraval F, et al. The impact of the prevention programme of hepatitis C over more than a decade: The French experience. J Viral Hepat. 2010;17(6):435-43. | Intervention |
| Desbois D, Vaghefi P, Savary J, Dussaix E, Roque-Afonso AM. Sensitivity of a rapid immuno-chromatographic test for Hepatitis C antibodies detection. J Clin Virol. 2008;41(2):129-33. | Intervention |
| Deuffic-Burban S, Deltenre P, Louvet A, Canva V, Dharancy S, Hollebecque A, et al. Impact of viral eradication on mortality related to hepatitis C: A modeling approach in France. J Hepatol. 2008;49(2):175-83. | Comparator |
| Ditah I, Al Bawardy B, Gonzalez HC, Saberi B, Ditah C, Kamath PS, et al. Lack of health insurance limits the benefits of hepatitis C virus screening: insights from the National Health and Nutrition Examination Hepatitis C follow-up study. Am J Gastroenterol. 2015 Aug;110(8):1126-33. | Population |
| Dokubo EK, Evans J, Winkelman V, Cyrus S, Tobler LH, Asher A, et al. Comparison of Hepatitis C Virus RNA and antibody detection in dried blood spots and plasma specimens. J Clin Virol. 2014 Apr;59(4):223-7. | Reference standard |
| Ecemis T, Akcali S, Erbay DP, Sanlidag T. The threshold value of anti-HCV test in the diagnosis of HCV infection. Turkiye Klinikleri Journal of Medical Sciences. 2012;32(6):1648-52. | Not in French or English |
| Echevarria JM, Avellon A, Jonas G, Hausmann M, Vockel A, Kapprell HP. Sensitivity of a modified version of the ARCHITECT Anti-HCV test in detecting samples with immunoblot-confirmed, low-level antibody to hepatitis C virus. J Clin Virol. 2006;35(4):368-72. | Intervention |
| Eckman MH, Talal AH, Gordon SC, Schiff E, Sherman KE. Cost-effectiveness of screening for chronic hepatitis C infection in the United States. Clin Infect Dis. 2013;56(10):1382-93. | Setting |
| Edeh J, Spalding P. Screening for HIV, HBV and HCV markers among drug users in treatment in rural south-east England. J Public Health Med. 2000 Dec;22(4):531-9. | Intervention |
| Edlin BR. Hepatitis C screening: getting it right. Hepatology. 2013 Apr;57(4):1644-50. | Editorial or review |
| El-Sayed ZM, el-Adrosy H. Recent approach for diagnosis of early HCV infection. Egypt J Immunol. 2004;11(1):123-9. | Population |
| El-Sherif A, Elbahrawy A, Aboelfotoh A, Abdelkarim M, Saied Mohammad AG, Abdallah AM, et al. High false-negative rate of anti-HCV among Egyptian patients on regular hemodialysis. Hemodial Int. 2012;16(3):420-7. | Population |
| Esteban JI, van Helden J, Alborino F, Burgisser P, Cellerai C, Pantaleo G, et al. Multicenter evaluation of the Elecsys anti-HCV II assay for the diagnosis of hepatitis C virus infection. J Med Virol. 2013 Aug;85(8):1362-8. | Reference standard |
| Faye B, Irurita VF. Balancing perspective: The response to feelings of being condemned with the hepatitis C virus. Journal of Substance Use. 2003;8(2):92-103. | Intervention |
| Ferreira O, Passos AD. Factors associated with failure of clinical screening among blood donors who have altered serological results in the Centro Regional de Hemoterapia de | Outcomes |

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| Study | Reason for Exclusion |
|---|---|
| Ribeirao Preto. Rev bras hematol hemoter. 2012;34(6):411-5. | |
| Firdaus R, Saha K, Sadhukhan PC. Rapid immunoassay alone is insufficient for the detection of hepatitis C virus infection among high-risk population. J Viral Hepat. 2013 Apr;20(4):290-3. | Population |
| Ford PM, Pearson M, Sankar-Mistry P, Stevenson T, Bell D, Austin J. HIV, hepatitis C and risk behaviour in a Canadian medium-security federal penitentiary. QJM. 2000;93(2):113-9. | Intervention |
| Fralick M. Screening urged for hepatitis C but drug costs are prohibitive. CMAJ. 2014 Mar 18;186(5):329, 2014. | Editorial or review |
| Galel SA, Strong DM, Tegtmeier GE, Holland PV, Kuramoto IK, Kemper M, et al. Comparative yield of HCV RNA testing in blood donors screened by 2.0 versus 3.0 antibody assays. Transfusion. 2002 Nov;42(11):1507-13. | Reference standard |
| Gasiorowicz M, Hurie M, Russell A, Hoxie N, Vergeront J. Epidemiologic trends in infection, mortality, and transplants related to hepatitis C in Wisconsin. Wis Med J. 2006;105(1):34-9. | Intervention |
| Gaudy C, Thevenas C, Tichet J, Mariotte N, Goudeau A, Dubois F. Usefulness of the hepatitis C virus core antigen assay for screening of a population undergoing routine medical checkup. J Clin Microbiol. 2005 Apr;43(4):1722-6. | Population |
| Gibney L, Saquib N, Metzger J, Choudhury P, Siddiqui M, Hassan M. Human immunodeficiency virus, hepatitis B, C and D in Bangladesh's trucking industry: prevalence and risk factors. Int J Epidemiol. 2001 Aug;30(4):878-84. | Population |
| Glynn SA, Kleinman SH, Schreiber GB, Busch MP, Wright DJ, Smith JW, et al. Trends in incidence and prevalence of major transfusion-transmissible viral infections in US blood donors, 1991 to 1996. Retrovirus Epidemiology Donor Study (REDS). JAMA. 2000 Jul 12;284(2):229-35. | Intervention |
| Goncales FL, Jr., Stucchi RS, Pavan MH, Escanhoela CA, Yamanaka A, Magna LA, et al. A clinical, epidemological, laboratorial, histological and ultrasonographical evaluation of anti-HCV EIA-2 positive blood donors. Rev Inst Med Trop Sao Paulo. 2000 May;42(3):147-52. | Population |
| Gonzalez V, Martro E, Folch C, Esteve A, Matas L, Montoliu A, et al. Detection of hepatitis C virus antibodies in oral fluid specimens for prevalence studies. Eur J Clin Microbiol Infect Dis. 2008 Feb;27(2):121-6. | Population |
| Grando-Lemaire V, Goisset P, Sorge F, Trinchet JC, Castera L, Roulot D, et al. Hepatitis C virus screening in drug users in an addiction out-patient unit. Gastroenterol Clin Biol. 2002 Dec;26(12):1091-6. | Population |
| Grebely J, Bilodeau M, Feld JJ, Bruneau J, Fischer B, Raven JF, et al. The Second Canadian Symposium on hepatitis C virus: a call to action. Can J Gastroenterol. 2013 Nov;27(11):627-32. | Editorial or review |
| Grijalva MJ, Chiriboga RF, Vanhassel H, Arcos-Teran L. Improving the safety of the blood supply in Ecuador through external performance evaluation of serological screening of blood donors. J Clin Virol. 2005 Dec;34 Suppl 2:S47-52. | Outcomes |
| Guirgis M, Nusair F, Bu YM, Yan K, Zekry AT. Barriers faced by migrants in accessing healthcare for viral hepatitis infection. Intern Med J. 2012 May;42(5):491-6. | Population |
| Gunewardene R, Lampe L, Ilchef R. Prevalence of hepatitis C in two inpatient psychiatry populations. Australas. 2010 Aug;psychiatry. 18(4):330-4. | Outcomes |
| Gunn RA, Murray PJ, Ackers ML, Hardison WG, Margolis HS. Screening for chronic hepatitis B and C virus infections in an urban sexually transmitted disease clinic: rationale for integrating services. Sex Transm Dis. 2001 Mar;28(3):166-70. | Intervention |
| Haley RW, Fischer RP. Commercial tattooing as a potentially important source of hepatitis C infection. Clinical epidemiology of 626 consecutive patients unaware of their hepatitis C serologic status. Medicine (Baltimore). 2001 Mar;80(2):134-51. | Outcomes |
| Halim NK, Ajayi OI. Risk factors and seroprevalence of hepatitis C antibody in blood donors in | Intervention |

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| Study | Reason for Exclusion |
|---|---|
| Nigeria. East Afr Med J. 2000 Aug;77(8):410-2. | |
| Han X, Aho M, Vene S, Peltomaa M, Vaheri A, Vapalahti O. Evaluation of hepatitis C antibody testing in saliva specimens collected by two different systems in comparison with HCV antibody and HCV RNA in serum. J Med Virol. 2001;64(1):13-20. | Population |
| Hara M, Mori M, Hara T, Yamamoto K, Honda M, Nishizumi M. Risk of developing hepatocellular carcinoma according to the titer of antibody to hepatitis C virus. Hepatogastroenterology. 2001;48(38):498-501. | Comparator |
| Harris KA, Jr., Arnsten JH, Litwin AH. Successful integration of hepatitis C evaluation and treatment services with methadone maintenance. J Addict Med. 2010 Mar;4(1):20-6. | Outcomes |
| Hart R, Khalaf Y, Lawson R, Bickerstaff H, Taylor A, Braude P. Screening for HIV, hepatitis B and C infection in a population seeking assisted reproduction in an inner London hospital. BJOG. 2001 Jun;108(6):654-6. | Outcomes |
| Hatzakis A, Wait S, Bruix J, Buti M, Carballo M, Cavaleri M, et al. The state of hepatitis B and C in Europe: report from the hepatitis B and C summit conference. J Viral Hepat. 2011 Sep;18 Suppl 1:1-16. | Editorial or review |
| He J, Xiu B, Wang G, Chen K, Feng X, Song X, et al. Double-antigen sandwich ELISA for the detection of anti-hepatitis C virus antibodies. J Virol Methods. 2011 Jan;171(1):163-8. | Reference standard |
| Hennig H, Schlenke P, Kirchner H, Bauer I, Schulte-Kellinghaus B, Bludau H. Evaluation of newly developed microparticle enzyme immunoassays for the detection of HCV antibodies. Journal of Virological Methods. 2000;84(2):181-90. | Reference standard |
| Hewitt PE. Implications of notifying donors and recipients. Vox Sanguinis, Supplement. 2004;87(2):S1-S2. | Intervention |
| Hickman M, McDonald T, Judd A, Nichols T, Hope V, Skidmore S, et al. Increasing the uptake of hepatitis C virus testing among injecting drug users in specialist drug treatment and prison settings by using dried blood spots for diagnostic testing: a cluster randomized controlled trial. J Viral Hepat. 2008 Apr;15(4):250-4. | Intervention |
| Hitzler WE, Runkel S. Routine HCV PCR screening of blood donations to identify early HCV infection in blood donors lacking antibodies to HCV. Transfusion. 2001 Mar;41(3):333-7. | Intervention |
| Horne JA, Clements AJ, Drennan P, Stein K, Cramp ME. Screening for hepatitis C virus in the Dartmoor prison population: an observational study. J Public Health (Oxf). 2004 Dec;26(4):372-5. | Intervention |
| Horne PM, Mills R. Implications of the 2012 Centers for Disease Control and Prevention (CDC) guidelines for screening hepatitis C infection in the United States. Pract Gastroenterol. 2013;37(2):36-41. | Editorial or review |
| Hu KQ, Yang H, Lin YC, Lindsay KL, Redeker AG. Clinical Profiles of Chronic Hepatitis C in a Major County Medical Center Outpatient Setting in United States. Int J Med Sci. 2004;1(2):92-100. | Intervention |
| Huang WS, Lu SN, Wang JH, Lee CM, Tung HD, Chen TM, et al. Prediction of viremia for cases of hepatitis C virus (HCV) infection using a third-generation anti-HCV enzyme immunoassay test. Hepatogastroenterology. 2005 May;52(63):893-6. | Population |
| Icardi G, Ansaldi F, Bruzzone BM, Durando P, Lee S, De LC, et al. Novel approach to reduce the hepatitis C virus (HCV) window period: Clinical evaluation of a new enzyme-linked immunosorbent assay for HCV core antigen. J Clin Microbiol. 2001;39(9):3110-4. | Reference standard |
| Jafroodi M, Davoudi-Kiakalayeh A, Mohtasham-Amiri Z, Pourfathollah AA, Haghbin A. Trend in Prevalence of Hepatitis C Virus Infection among beta-thalassemia Major Patients: 10 Years of Experience in Iran. Int J Prev Med. 2015;6:89, 2015. | Outcomes |
| Jin F, Prestage GP, Matthews G, Zablotska I, Rawstorne P, Kippax SC, et al. Prevalence, incidence and risk factors for hepatitis C in homosexual men: data from two cohorts of HIV- | Population |

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| Study | Reason for Exclusion |
|---|---|
| negative and HIV-positive men in Sydney, Australia. Sex Transm Infect. 2010 Feb;86(1):25-8. | |
| Jones L, Atkinson A, Bates G, McCoy E, Porcellato L, Beynon C, et al. Views and experiences of hepatitis C testing and diagnosis among people who inject drugs: systematic review of qualitative research. Int J Drug Policy. 2014 Mar;25(2):204-11. | Editorial or review |
| Jordan AE, Masson CL, Mateu-Gelabert P, McKnight C, Pepper N, Bouche K, et al. Perceptions of drug users regarding Hepatitis C screening and care: A qualitative study. Harm Reduct J. 2013;10(1). | Population |
| Josset V, Chamouni P, Tavolacci MP, Merle V, Delbos V, Froment L, et al. Efficiency of hepatitis C virus screening before and after blood transfusion. Transfus Clin Biol. 2004 Oct;11(4):186-91. | Setting |
| Judd A, Parry J, Hickman M, McDonald T, Jordan L, Lewis K, et al. Evaluation of a modified commercial assay in detecting antibody to hepatitis C virus in oral fluids and dried blood spots. J Med Virol. 2003;71(1):49-55. | Population |
| Kaffashian A, Nokhodian Z, Kassaian N, Babak A, Yaran M, Shoaei P, et al. The experience of hepatitis C screening among prison inmates with drug injection history. Journal of Isfahan Medical School. 2011;28. | Not in French or English |
| Kanaan T, Liu A, Leroi M, Nanan R. A multicentre survey of hepatitis C awareness in a high-risk population. J Paediatr Child Health. 2013 Aug;49(8):649-53. | Intervention |
| Karimi M, Ghavanini AA. Seroprevalence of HBsAg, anti-HCV, and anti-HIV among haemophiliac patients in Shiraz, Iran. Haematologia (Budap). 2001;31(3):251-5. | Intervention |
| Kaur H, Dhanoa J, Pawar G. Hepatitis C infection amongst blood donors in Punjab - A 6 years study. Indian Journal of Hematology and Blood Transfusion. 2001;19(1):21-2. | Other |
| Kesli R, Ozdemir M, Kurtoglu MG, Baykan M, Baysal B. Evaluation and comparison of three different anti-hepatitis C virus antibody tests based on chemiluminescence and enzyme-linked immunosorbent assay methods used in the diagnosis of hepatitis C infections in Turkey. J Int Med Res. 2009 Sep;37(5):1420-9. | Outcomes |
| Kim AY, Nagami EH, Birch CE, Bowen MJ, Lauer GM, McGovern BH. A simple strategy to identify acute hepatitis C virus infection among newly incarcerated injection drug users. Hepatology. 2013 Mar;57(3):944-52. | Outcomes |
| Kim S, Kim JH, Yoon S, Park YH, Kim HS. Clinical performance evaluation of four automated chemiluminescence immunoassays for hepatitis C virus antibody detection. J Clin Microbiol. 2008 Dec;46(12):3919-23. | Reference standard |
| Koretz RL, Lin KW, Ioannidis JPA, Lenzer J. Is widespread screening for hepatitis C justified? BMJ (Online). 2015;350. | Editorial or review |
| Kumar R, Gupta S, Kaur A, Gupta M. Individual donor-nucleic acid testing for human immunodeficiency virus-1, hepatitis C virus and hepatitis B virus and its role in blood safety. Asian J Transfus Sci. 2015 Jul-Dec;9(2):199-202 | Outcomes |
| Kuncio DE, Newbern EC, Fernandez-Vina MH, Herdman B, Johnson CC, Viner KM. Comparison of risk-based hepatitis C screening and the true seroprevalence in an urban prison system. J Urban Health. 2015 Apr;92(2):379-86. | Outcomes |
| Kuo YH, Chen PF, Wang JH, Chang KC, Kee KM, Tsai MC, et al. Comparison stratagems of post-screening management of anti-HCV-positive community residents: Simple notification, active referral, or accessible medical care. PLoS ONE. 2015;10(5). | Comparator |
| Kupek E, Petry A. Changes in the prevalence, Incidence and residual risk for HIV and hepatitis C virus in southern brazilian blood donors since the implementation of NAT screening. Revista da Sociedade Brasileira de Medicina Tropical. 2014;47(4):418-25. | Population |
| Kwon JA, Lee H, Kap NL, Chae K, Lee S, Lee DK, et al. High diagnostic accuracy of antigen microarray for sensitive detection of hepatitis C virus infection. Clin Chem. 2008;54(2):424-8. | Reference standard |

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| Study | Reason for Exclusion |
|---|---|
| Lambert N. Value of HCV antigen-antibody combined HCV assay in hepatitis C diagnosis. Dev Biol (Basel). 2007;127:113-21. | Editorial or review |
| Laperche S, Le Mareec N, Girault A, Bouchardeau F, Servant-Delmas A, Maniez-Montreuil M, et al. Simultaneous detection of hepatitis C virus (HCV) core antigen and anti-HCV antibodies improves the early detection of HCV infection. J Clin Microbiol. 2005 Aug;43(8):3877-83. | Reference standard |
| Laperche S, Elghouzzi MH, Morel P, Asso-Bonnet M, Le Marrec N, Girault A, et al. Is an assay for simultaneous detection of hepatitis C virus core antigen and antibody a valuable alternative to nucleic acid testing? Transfusion. 2005 Dec;45(12):1965-72. | Population |
| Laperche S, Boukatou G, Kouegnigan L, Nebie Y, Boulahi MO, Tagny CT, et al. Transfusion safety on the African continent: an international quality control of virus testing in blood banks. Transfusion. 2009 Aug;49(8):1600-8. | Reference standard |
| Laperche S, Nubling CM, Stramer SL, Brojer E, Grabarczyk P, Yoshizawa H, et al. Sensitivity of hepatitis C virus core antigen and antibody combination assays in a global panel of window period samples. Transfusion. 2015;55(10):2489-98. | Reference standard |
| LaTorre G, De Vito E, Langiano E, Petta P, Colarossi G, Cipriani L, et al. Epidemiology of hepatitis C virus antibodies in blood donors from the province of Latina, Italy. Eur J Epidemiol. 2003;18(7):691-4. | Outcomes |
| Laufer CB, Carroll MB. Hepatitis C Virus in the US military retiree population: to screen, or not to screen? J Clin Med Res. 2015 Oct;7(10):757-61. | Outcomes |
| Lee SR, Peterson J, Niven P, Bahl C, Page E, DeLeys R, et al. Efficacy of a hepatitis C virus core antigen enzyme-linked immunosorbent assay for the identification of 'window-phase' blood donations. Vox Sang. 2001 Jan;80(1):19-23. | Reference standard |
| Lee SR, Yearwood GD, Guillon GB, Kurtz LA, Fischl M, Friel T, et al. Evaluation of a rapid, point-of-care test device for the diagnosis of hepatitis C infection. J Clin Virol. 2010 May;48(1):15-7. | Intervention |
| Lee SR, Kardos KW, Schiff E, Berne CA, Mounzer K, Banks AT, et al. Evaluation of a new, rapid test for detecting HCV infection, suitable for use with blood or oral fluid. J Virol Methods. 2011 Mar;172(1-2):27-31. | Population |
| Letowska M, Brojer E, Mikulska M, Gronowska A, Rosiek A. Hepatitis C core antigen in Polish blood donors. Transfusion. 2004 Jul;44(7):1067-71. | Intervention |
| Linas BP, Barter DM, Leff JA, Assoumou SA, Salomon JA, Weinstein MC, et al. The hepatitis C cascade of care: Identifying priorities to improve clinical outcomes. PLoS ONE. 2014;9(5). | Intervention |
| Macalino GE, Dhawan D, Rich JD. A missed opportunity: Hepatitis C screening of prisoners. Am J Public Health. 2005;95(10):1739-40. | Outcomes |
| Macedo G, Lopes S, Barroso S, Malheiro L, Ferreira A, Campos M, et al. Implementation of screening and preventive strategies in liver transplant candidates. Transplant Proc. 2003;35(3):1115. | Population |
| Maclean R, Fox E. Universal hepatitis C screening in genitourinary medicine. Int J STD AIDS. 2010 Jul;21(7):504-5. | Intervention |
| Maio G, d'Argenio P, Stroffolini T, Bozza A, Sacco L, Tosti ME, et al. Hepatitis C virus infection and alanine transaminase levels in the general population: a survey in a southern Italian town. J Hepatol. 2000 Jul;33(1):116-20. | Population |
| Maity S, Nandi S, Biswas S, Sadhukhan SK, Saha MK. Performance and diagnostic usefulness of commercially available enzyme linked immunosorbent assay and rapid kits for detection of HIV, HBV and HCV in India. Virol J. 2012;9:290, 2012. | Reference standard |
| Makroo RN, Raina V, Goyal N, Kaushik V. Effectiveness of screening blood for anti HBc and anti HCV on post transfusion hepatitis on multiply transfused patients. Indian Journal of Hematology and Blood Transfusion. 2001;19(2):49-50. | Other |

## Table 5: List of Studies Excluded From the Systematic Review — November 2015 Database Search

| Study | Reason for Exclusion |
|---|---|
| Mallette C, Flynn MA, Promrat K. Outcome of screening for hepatitis C virus infection based on risk factors. Am J Gastroenterol. 2008 Jan;103(1):131-7. | Study design |
| Mark KE, Murray PJ, Callahan DB, Gunn RA. Medical care and alcohol use after testing hepatitis C antibody positive at STD clinic and HIV test site screening programs. Public Health Rep. 2007 Jan;122(1):37-43. | Study design |
| Marufu M, Williams H, Hill SL, Tibble J, Verma S. Gender differences in hepatitis C seroprevalence and suboptimal vaccination and hepatology services uptake amongst substance misusers. J Med Virol. 2012 Nov;84(11):1737-43. | Outcomes |
| Masson CL, Delucchi KL, McKnight C, Hettema J, Khalili M, Min A, et al. A randomized trial of a hepatitis care coordination model in methadone maintenance treatment. Am J Public Health. 2013 Oct;103(10):e81-e88. | Intervention |
| McDonald SA, Hutchinson SJ, Palmateer NE, Allen E, Cameron SO, Goldberg DJ, et al. Decrease in health-related quality of life associated with awareness of hepatitis C virus infection among people who inject drugs in Scotland. J Hepatol. 2013 Mar;58(3):460-6. | Intervention |
| Merchant RC, Baird JR, Liu T, Taylor LE, Montague BT, Nirenberg TD. Brief intervention to increase emergency department uptake of combined rapid human immunodeficiency virus and hepatitis C screening among a drug misusing population. Acad Emerg Med. 2014 Jul;21(7):752-67. | Intervention |
| Mihaila RG, Rezi EC, Nedelcu L, Fratila O, Domnariu C, Deac M, et al. The prevalence and the clinical and biological characterstics of the patients with chronic liver diseases in Transylvania - Multicentric epidemiological study. Arch Balkan Med Union. 2010;45(2):111-5. | Intervention |
| Miyazaki T, Honda A, Ikegami T, Hara T, Saitoh Y, Hirayama T, et al. The associated markers and their limitations for the primary screening of HCV carriers in public health examination. Hepatol Res. 2009;39(7):664-74. | Intervention |
| Mohammadali F, Pourfathollah AA. Changes in frequency of HBV, HCV, HIV and syphilis infections among blood donors in Tehran province 2005 - 2011. Arch Iran Med. 2014 Sep;17(9):613-20. | Outcomes |
| Mohamud HS, Mohamed DH, Alqahtani FH, Almajid FM, Alswat K, Somily AM. Two years' experience of implementing molecular screening of hepatitis B virus, hepatitis C virus and human immunodeficiency virus 1, 2 in Riyadh blood donors. Transfus Apher Sci. 2015 Oct 13. | Intervention |
| Moller JM, Krarup HB. Diagnosis of acute hepatitis C: anti-HCV or HCV-RNA? Scand J Gastroenterol. 2003 May;38(5):556-8. | Intervention |
| Moorthy M, Daniel HD, Kurian G, Abraham P. An evaluation of saliva as an alternative to plasma for the detection of hepatitis C virus antibodies. Indian J Med Microbiol. 2008 Oct;26(4):327-32. | Population |
| Morota K, Fujinami R, Kinukawa H, Machida T, Ohno K, Saegusa H, et al. A new sensitive and automated chemiluminescent microparticle immunoassay for quantitative determination of hepatitis C virus core antigen. Journal of Virological Methods. 2009;157(1):8-14. | Reference standard |
| Mullis CE, Laeyendecker O, Reynolds SJ, Ocama P, Quinn J, Boaz I, et al. High frequency of false-positive hepatitis C virus enzyme-linked immunosorbent assay in Rakai, Uganda. Clin Infect Dis. 2013 Dec;57(12):1747-50. | Population |
| Ndako JA, Olabode OA, Echeonwu GON, Chukwuekezie J, Ebo CC, Salihu EA. Occurrence of antibodies against hepatitis C virus (HCV) among alcoholics. African Journal of Biotechnology. 2010;9(52):8908-12. | Population |
| Nemecek V, Toulcova A, Summerova M, Koning J, Turek P. Screening and confirmation of blood donors at the Czech Republic. Transfuze Dnes. 2001;7(1):19-23. | Not in English or French |
| Nikolaeva IA, Mahboudi F, Chevalier A, Khalili G, Khadem A, Somova AV, et al. Evaluation of a new anti-hiv1/2 elisa-hiv 1/2 rec diagnostic kit based on e. Coli derived soluble recombinant | Intervention |

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| Study | Reason for Exclusion |
|---|---|
| proteins: Experience of an international study. Iranian Journal of Medical Sciences. 2003;28(1):37-42. | |
| Noori S, Gol-Mohamadi A, Sarbazi MR, Safaee A, Farsar AR. Epidemiological features of hepatitis B and C infection in a high risk population: results of screening programs. Gastroenterol. 2013;hepatol. bed bench. 6(3):136-40. | Population |
| Nubling CM, Unger G, Chudy M, Raia S, Lower J. Sensitivity of HCV core antigen and HCV RNA detection in the early infection phase. Transfusion. 2002 Aug;42(8):1037-45. | Population |
| O'Brien JM, Kruzel KE, Wandell MG, Vinogradov IV, Sheagren JN, Frank AP. Detection of hepatitis C antibody with at-home collection kits using an innovative laboratory algorithm. Infect Dis Clin Pract. 2001;10(9):474-80. | Intervention |
| O'Brien SF, Fan W, Xi G, Yi QL, Goldman M, Fearon MA, et al. Declining hepatitis C rates in first-time blood donors: Insight from surveillance and case-control risk factor studies. Transfusion. 2008;48(5):902-9. | Outcomes |
| Odari EO, Budambula NLM, Nitschko H. Evaluation of an antigen-antibody "combination" enzyme linked immunosorbent assay for diagnosis of hepatitis C virus infections. Ethiop J Health Sci. 2014 Oct;24(4):343-52. | Population |
| Operskalski EA, Mosley JW, Tobler LH, Fiebig EW, Nowicki MJ, Mimms LT, et al. HCV viral load in anti-HCV-reactive donors and infectivity for their recipients. Transfusion. 2003;43(10):1433-41. | Intervention |
| O'Sullivan MJ, Evoy D, O'Donnell C, Rajpal PK, Cannon B, Kenny-Walsh L, et al. Gallstones and laparoscopic cholecystectomy in hepatitis C patients. Ir Med J. 2001 Apr;94(4):114-7. | Intervention |
| Paydas S, Ergin M, Tanriverdi K, Yavuz S, Disel U, Kilic NB, et al. Detection of hepatitis C virus RNA in paraffin-embedded tissues from patients with non-Hodgkin's lymphoma. Am J Hematol. 2004 Jul;76(3):252-7. | Study design |
| Pepas L, Macmahon E, El TT, Khalaf Y, Braude P. Viral screening before each cycle of assisted conception treatment is expensive and unnecessary: a survey of results from a UK inner city clinic. Hum Fertil (Camb). 2011 Dec;14(4):224-9. | Outcomes |
| Pereira A, Sanz C. A model of the health and economic impact of posttransfusion hepatitis C: Application to cost-effectiveness analysis of further expansion of HCV screening protocols. Transfusion. 2000;40(10):1182-91. | Population |
| Pereira A. Health and economic consequences of HCV lookback. Transfusion. 2001 Jun;41(6):832-9. | Population |
| Perreault D. Hepatitis C: a study predicts a costly future if nothing is done now. Perspect Infirm. 2014 Sep;11(4):14, 2014-14, 2Oct. | Editorial or review |
| Perumalswami PV, Factor SH, Kapelusznik L, Friedman SL, Pan CQ, Chang C, et al. Hepatitis Outreach Network: A practical strategy for hepatitis screening with linkage to care in foreign-born communities. J Hepatol. 2013;58(5):890-7. | Outcomes |
| Pillonel J, Laperche S, Agents Transmissibles par Transfusion de la de la Société française de transfusion sanguine, l'Établissement français du sang, Centre de transfusion sanguine des armées. Trends in residual risk of transfusion-transmitted viral infections (HIV, HCV, HBV) in France between 1992 and 2002 and impact of viral genome screening (Nucleic Acid Testing). Transfus Clin Biol. 2004 Apr;11(2):81-6. | Outcomes |
| Ponamgi SPD, Chandra M, Naresh KY, Rahamathulla S, Narasu L, Habibullah CM, et al. Genotype analysis and assessment of antigenic sensitivity for recombinant HCV proteins by indigenous SIBA for detection of Hepatitis C Virus infection: A comparison with 3rd EIA and RT-PCR. Indian Journal of Biotechnology. 2009;8(1):33-9. | Population |
| Pradat P, Caillat-Vallet E, Sahajian F, Bailly F, Excler G, Sepetjan M, et al. Prevalence of hepatitis C infection among general practice patients in the Lyon area, France. European | Reference standard |

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| Study | Reason for Exclusion |
|---|---|
| Journal of Epidemiology. 2001;17(1):47-51. | |
| Raghuraman S, Subramaniam T, Daniel D, Sridharan G, Abraham P. Occurrence of false positives during testing for antibodies to hepatitis C virus among volunteer blood donors in India. J Clin Microbiol. 2003;41(4):1788-90. | Reference standard |
| Rao HY, Ren FR, Guan WL, Houde M, Du SC, Liu CL, et al. Evaluation of the performance of the EIAgen HCV test for detection of hepatitis C virus infection. Journal of Virological Methods. 2009;162(1-2):203-7. | Reference standard |
| Ravera G, Bottaro LC, Franceschini M, Morando A, De PM, Zare M, et al. Reliability and diagnostic use of a test for the search of the hepatitis C virus Ag (AgHCV). Hepatogastroenterology. 2006 Sep;53(71):753-6. | Reference standard |
| Re V, Gallego S, Trevino E, Barbas G, Dominguez C, Elbarcha O, et al. Evaluation of five screening tests licensed in Argentina for detection of hepatitis C virus antibodies. Mem Inst Oswaldo Cruz. 2005 May;100(3):303-7. | Reference standard |
| Reid CT, De GC, Hall W, Collins P, Lally A, Kirby B. Is universal screening for hepatitis C infection prior to commencing antitumour necrosis factor-alpha therapy necessary? Br J Dermatol. 2013 Dec;169(6):1319-21. | Outcomes |
| Rein DB, Wittenborn JS, Weinbaum CM, Sabin M, Smith BD, Lesesne SB. Forecasting the morbidity and mortality associated with prevalent cases of pre-cirrhotic chronic hepatitis C in the United States. Dig Liver Dis. 2011 Jan;43(1):66-72. | Intervention |
| Remesar M, Gamba C, Kuperman S, Marcosa MA, Miguez G, Caldarola S, et al. Antibodies to hepatitis C and other viral markersin multi-transfused patients from Argentina. J Clin Virol. 2005 Dec;34 Suppl 2:S20-6. | Population |
| Rhodes SD, DiClemente RJ, Yee LJ, Hergenrather KC. Factors associated with testing for hepatitis C in an internet-recruited sample of men who have sex with men. Sex Transm Dis. 2001;28(9):515-20. | Outcomes |
| Rice S. Screening for hepatitis C raises ethical, cost issues. Mod Healthc. 2014 Mar 10;44(10):11, 2014. | Editorial or review |
| Rifai MA, Moles JK, Lehman LP, Van Der Linden BJ. Hepatitis C screening and treatment outcomes in patients with substance use/dependence disorders. Psychosomatics. 2006;47(2):112-21. | Comparator |
| Roblin DW, Smith BD, Weinbaum CM, Sabin ME. HCV screening practices and prevalence in an MCO, 2000-2007. Am J Manag Care. 2011;17(8):548-55. | Population |
| Rosenberg SD, Goldberg RW, Dixon LB, Wolford GL, Slade EP, Himelhoch S, et al. Assessing the STIRR model of best practices for blood-borne infections of clients with severe mental illness. Psychiatr Serv [Internet]. 2010 Sep [cited 2015 Dec 9];61(9):885-91. | Setting |
| Ross RS, Stambouli O, Gruner N, Marcus U, Cai W, Zhang W, et al. Detection of infections with hepatitis B virus, hepatitis C virus, and human immunodeficiency virus by analyses of dried blood spots - performance characteristics of the ARCHITECT system and two commercial assays for nucleic acid amplification. Virology Journal. 2015;10(1). | Reference standard |
| Roudot-Thoraval F, Monnet E, Mercet P, Bastie A, Dhumeaux D, Miguet JP. Strategies of hepatitis C screening in general practice. Results of a two-center randomized trial. Gastroenterol Clin Biol. 2000 Nov;24(11):1037-41. | Intervention |
| Rouet F, Deleplancque L, Mboumba BB, Sica J, Mouinga-Ondeme A, Liegeois F, et al. Usefulness of a fourth generation ELISA assay for the reliable identification of HCV infection in HIV-positive adults from Gabon (Central Africa). PLoS ONE. 2015;10(1):e0116975, 2015. | Population |
| Sagnelli E, Starnini G, Sagnelli C, Monarca R, Zumbo G, Pontali E, et al. Blood born viral infections, sexually transmitted diseases and latent tuberculosis in italian prisons: a preliminary | Outcomes |

## Table 5: List of Studies Excluded From the Systematic Review — November 2015 Database Search

| Study | Reason for Exclusion |
|---|---|
| report of a large multicenter study. Eur Rev Med Pharmacol Sci. 2012 Dec;16(15):2142-6. | |
| Sahajian F, Bailly F, Caillat-Vallet E, Pradat P, Excler G, Sepetjan M, et al. Medical follow-up of patients with positive serology for hepatitis C virus. Gastroenterol Clin Biol. 2001 Mar;25(3):262-7. | Outcomes |
| Sahajian F, Vanhems P, Bailly F, Fabry J, Trepo C, Sepetjan M. Screening campaign of hepatitis C among underprivileged people consulting in health centres of Lyon area, France. Eur J Public Health. 2007 Jun;17(3):263-71. | Study design |
| Sahajian F, Bailly F, Vanhems P, Fantino B, Vannier-Nitenberg C, Fabry J, et al. A randomized trial of viral hepatitis prevention among underprivileged people in the Lyon area of France. J Public Health (Oxf). 2011 Jun;33(2):182-92. | Outcomes |
| Sakarya S, Oncu S, Ozturk B, Oncu S. Effect of preventive applications on prevalence of hepatitis B virus and hepatitis C virus infections in West Turkey. Saudi Med J. 2004 Aug;25(8):1070-2. | Intervention |
| Salvaneschi L, Del FC, Perotti C. Screening and diagnosis of blood-borne infections in Italy. Tumori. 2001;87(2):S47-S48. | Editorial or review |
| Sarov B, Novack L, Beer N, Safi J, Soliman H, Pliskin JS, et al. Feasibility and cost-benefit of implementing pooled screening for HCVAg in small blood bank settings. Transfus Med. 2007;17(6):479-87. | Population |
| Satoskar R, Reau N. Potential consequences of healthcare recommendations: a focus on the U.S. Preventive Services Task Force. Hepatology. 2013 Jul;58(1):422-7. | Editorial or review |
| Scalioni LP, Cruz HM, de Paula VS, Miguel JC, Marques VA, Villela-Nogueira CA, et al. Performance of rapid hepatitis C virus antibody assays among high- and low-risk populations. J Clin Virol. 2014 Jul;60(3):200-5. | Intervention |
| Schroter M, Schafer P, Zollner B, Polywka S, Laufs R, Feucht HH. Strategies for reliable diagnosis of hepatitis C infection: the need for a serological confirmatory assay. J Med Virol. 2001 Jul;64(3):320-4. | Intervention |
| Scott C, Day S, Low E, Sullivan A, Atkins M, Asboe D. Unselected hepatitis C screening of men who have sex with men attending sexual health clinics. J Infect. 2010;60(5):351-3. | Intervention |
| Seedat F, Hargreaves S, Friedland JS. Engaging new migrants in infectious disease screening: A qualitative semi-structured interview study of UK migrant community health-care leads. PLoS ONE. 2014;9(10). | Population |
| Seremba E, Ocama P, Opio CK, Kagimu M, Thomas DL, Yuan HJ, et al. Poor performance of hepatitis C antibody tests in hospital patients in Uganda. J Med Virol. 2010 Aug;82(8):1371-8. | Population |
| Shan H, Ren FR, Zhao HY, Zhang YZ, Wen GX, Yao FZ, et al. A multi-Chinese blood center study testing serologic-negative donor samples for hepatitis C virus and human immunodeficiency virus with nucleic acid testing. Transfusion. 2007 Nov;47(11):2011-6. | Reference standard |
| Sharma M, Al KS, John AK, Al DN, Ullah WH, Babu TR, et al. Screening for hepatitis C in average and high-risk populations of Qatar using rapid point-of-care testing. United European Gastroenterol J. 2015 Aug;3(4):364-70. | Population |
| Singer ME, Younossi ZM. Cost effectiveness of screening for hepatitis C virus in asymptomatic, average-risk adults. Am J Med. 2001 Dec 1;111(8):614-21. | Setting |
| Smith BD, Morgan RL, Beckett GA, Falck-Ytter Y, Holtzman D, Ward JW. Hepatitis C virus testing of persons born during 1945-1965: recommendations from the Centers for Disease Control and Prevention. Ann Intern Med. 2012 Dec 4;157(11):817-22. | Guideline |
| Sookoian S, Castano G. Evaluation of a third generation anti-HCV assay in predicting viremia in patients with positive HCV antibodies. Ann Hepatol. 2002 Oct;1(4):179-82. | Reference standard |
| Soulier A, Poiteau L, Rosa I, Hezode C, Roudot-Thoraval F, Pawlotsky JM, et al. Dried Blood Spots: A Tool to Ensure Broad Access to Hepatitis C Screening, Diagnosis, and Treatment | Reference standard |

## Table 5: List of Studies Excluded From the Systematic Review — November 2015 Database Search

| Study | Reason for Exclusion |
|---|---|
| Monitoring. J Infect Dis. 2015 Sep 2. | |
| Stein K, Dalziel K, Walker A, McIntyre L, Jenkins B, Horne J, et al. Screening for hepatitis C among injecting drug users and in genitourinary medicine clinics: systematic reviews of effectiveness, modelling study and national survey of current practice. Health Technol Assess. 2002;6(31):1-122. | Editorial or review |
| Sultan M, Zaman MW, Begum HA, Hyder S. Declining trend of sero-prevalence of HBV, HCV and syphilis markers in selected blood donors due to mandatory blood screening: A comprehensive report from a Nationally Launched Blood Screening Programme in Bangladesh (2001 to 2003). Bangladesh Renal Journal. 2003;22(2):44-8. | Outcomes |
| Swellam M, Mahmoud MS, Ali AA. Diagnosis of hepatitis C virus infection by enzyme-linked immunosorbent assay and reverse transcriptase-nested polymerase chain reaction: a comparative evaluation. IUBMB Life. 2011 Jun;63(6):430-4. | Population |
| Sypsa V, Hadjipaschali E, Hatzakis A. Prevalence, risk factors and evaluation of a screening strategy for chronic hepatitis C and B virus infections in healthy company employees. Eur J Epidemiol. 2001;17(8):721-8. | Outcomes |
| Tagny CT, Mbanya D, Murphy EL, Lefrere JJ, Laperche S. Screening for hepatitis C virus infection in a high prevalence country by an antigen/antibody combination assay versus a rapid test. J Virol Methods. 2014 Apr;199:119-23, | Reference standard |
| Tejada-Strop A, Drobeniuc J, Mixson-Hayden T, Forbi JC, Le NT, Li L, et al. Disparate detection outcomes for anti-HCV IgG and HCV RNA in dried blood spots. J Virol Methods. 2015 Feb;212:66-70. | Editorial or review |
| Tillmann HL, Wiegand J, Glomb I, Jelineck A, Picchio G, Wedemeyer H, et al. Diagnostic algorithm for chronic hepatitis C virus infection: role of the new HCV-core antigen assay. Z Gastroenterol. 2005 Jan;43(1):11-6. | Population |
| Tiwari AK, Pandey PK, Negi A, Bagga R, Shanker A, Baveja U, et al. Establishing a sample-to cut-off ratio for lab-diagnosis of hepatitis C virus in Indian context. Asian J Transfus Sci. 2015 Jul;9(2):185-8. | Population |
| Tobler LH, Stramer SL, Lee SR, Masecar BL, Peterson JE, Davis EA, et al. Impact of HCV 3.0 EIA relative to HCV 2.0 EIA on blood-donor screening. Transfusion. 2003 Oct;43(10):1452-9. | Intervention |
| Tobler LH, Stramer SL, Lee SR, Baggett D, Wright D, Hirschkorn D, et al. Performance of ORTHO HCV core antigen and trak-CTM assays for detection of viraemia in pre-seroconversion plasma and whole blood donors. Vox Sang. 2005;89(4):201-7. | Reference standard |
| Tomaszewski KJ, Deniz B, Tomanovich P, Graham CS. Comparison of current US risk strategy to screen for hepatitis C virus with a hypothetical targeted birth cohort strategy. Am J Public Health. 2012 Nov;102(11):e101-e106. | Outcomes |
| Touzet S, Chapuis F, Colin C. Evaluation of the methodological aspects of screening: The case of screening for hepatitis C. Gastroenterol Clin Biol. 2000;24(6-7):631-6. | Editorial or review |
| Tramarin A, Gennaro N, Compostella FA, Gallo C, Wendelaar Bonga LJ, Postma MJ. HCV screening to enable early treatment of hepatitis C: a mathematical model to analyse costs and outcomes in two populations. Curr Pharm Des. 2008;14(17):1655-60. | Setting |
| Trepka MJ, Zhang G, Leguen F, Obiaja K, Malow RM, De La RM. Benefits and adverse effects of hepatitis C screening: Early results of a screening program. Journal of Public Health Management and Practice. 2007;13(3):263-9. | Comparator |
| Trooskin SB, Poceta J, Towey CM, Yolken A, Rose JS, Luqman NL, et al. Results from a Geographically Focused, Community-Based HCV Screening, Linkage-to-Care and Patient Navigation Program. J Gen Intern Med. 2015;30(7):950-7. | Comparator |
| Tsai PS, Chang CJ, Chen KT, Chang KC, Hung SF, Wang JH, et al. Acquirement and disappearance of HBsAg and anti-HCV in an aged population: a follow-up study in an endemic | Outcomes |

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| Study | Reason for Exclusion |
|---|---|
| township. Liver Int. 2011 Aug;31(7):971-9. | |
| Tsui JI, Vittinghoff E, Hahn JA, Evans JL, Davidson PJ, Page K. Risk behaviors after hepatitis C virus seroconversion in young injection drug users in San Francisco. Drug Alcohol Depend. 2009 Nov 1;105(1-2):160-3. | Comparator |
| Tuke PW, Grant PR, Waite J, Kitchen AD, Eglin RP, Tedder RS. Hepatitis C virus window-phase infections: closing the window on hepatitis C virus. Transfusion. 2008 Apr;48(4):594-600. | Intervention |
| Tulsiani S, Choudhury N, Desai P, Shah R, Mathur A, Harimoorthy V, et al. True positivity of anti-Hepatitis C Virus Enzyme-linked immunosorbent assay reactive blood donors: A prospective study done in western India. Asian Journal of Transfusion Science. 2012 Jul;6(2):165-8. | Reference standard |
| Turner BJ, Taylor BS, Hanson JT, Perez ME, Hernandez L, Villarreal R, et al. Implementing hospital-based baby boomer hepatitis C virus screening and linkage to care: Strategies, results, and costs. J Hosp Med. 2015 Aug;10(8):510-6. | Outcomes |
| Tynell E, Norda R, Ekermo B, Sanner M, Andersson S, Bjorkman A. False-reactive microbiologic screening test results in Swedish blood donors-how big is the problem? A survey among blood centers and deferred donors. Transfusion. 2007 Jan;47(1):80-9. | Reference standard |
| Udeagu Pratt CC, Paone D, Carter RJ, Layton MC. Hepatitis C screening and management practices: A survey of drug treatment and syringe exchange programs in New York City. Am J Public Health. 2002;92(8):1254-6. | Intervention |
| Ur Rahman M, Akhtar GN, Qadeer M, Shams T, Usmani A, Lodhi Y. Safe blood begins with safe donors. Pakistan Journal of Medical Sciences. 2003;19(3):161-8. | Outcomes |
| Urbanus AT, van de Laar TJ, van den Hoek A, Zuure FR, Speksnijder AG, Baaten GG, et al. Hepatitis C in the general population of various ethnic origins living in the Netherlands: should non-Western migrants be screened? J Hepatol. 2011 Dec;55(6):1207-14. | Outcomes |
| Valcavi P, Medici MC, Casula F, Arcangeletti MC, De CF, Pinardi F, et al. Evaluation of a total hepatitis C virus (HCV) core antigen assay for the detection of antigenaemia in anti-HCV positive individuals. J Med Virol. 2004 Jul;73(3):397-403. | Intervention |
| van Doornum GJ, Lodder A, Buimer M, van Ameijden EJ, Bruisten S. Evaluation of hepatitis C antibody testing in saliva specimens collected by two different systems in comparison with HCV antibody and HCV RNA in serum. J Med Virol. 2001 May;64(1):13-20. | Population |
| Varache S, Narbonne V, Jousse-Joulin S, Guennoc X, Dougados M, Daures JP, et al. Is routine viral screening useful in patients with recent-onset polyarthritis of a duration of at least 6 weeks? Results from a nationwide longitudinal prospective cohort study. Arthritis Care Res (Hoboken). 2011 Nov;63(11):1565-70. | Intervention |
| Vermeersch P, Van Ranst M, Lagrou K. Validation of a strategy for HCV antibody testing with two enzyme immunoassays in a routine clinical laboratory. J Clin Virol. 2008 Aug;42(4):394-8. | Comparator |
| Vermeiren APA, Dukers-Muijrers NHTM, van Loo I, Stals F, van Dam Ton Ambergen DW, Hoebe CJPA. Identification of Hidden Key Hepatitis C Populations: An Evaluation of Screening Practices Using Mixed Epidemiological Methods. PLoS ONE. 2012;7(12). | Outcomes |
| Vermeulen M, Lelie N, Sykes W, Crookes R, Swanevelder J, Gaggia L, et al. Impact of individual-donation nucleic acid testing on risk of human immunodeficiency virus, hepatitis B virus, and hepatitis C virus transmission by blood transfusion in South Africa. Transfusion. 2009 Jun;49(6):1115-25. | Intervention |
| Vo MT, Bruhn R, Kaidarova Z, Custer BS, Murphy EL, Bloch EM. A retrospective analysis of false-positive infectious screening results in blood donors. Transfusion. 2015 Oct 28. | Outcomes |
| Walter SR, Thein HH, Gidding HF, Amin J, Law MG, George J, et al. Risk factors for hepatocellular carcinoma in a cohort infected with hepatitis B or C. J Gastroenterol Hepatol. | Population |

## Table 5: List of Studies Excluded From the Systematic Review — November 2015 Database Search

| Study | Reason for Exclusion |
|---|---|
| 2011 Dec;26(12):1757-64. | |
| Wand H, Iversen J, Wilson D, Topp L, Maher L. Developing and validating a scoring tool for identifying people who inject drugs at increased risk of hepatitis C virus infection. BMJ Open. 2012;2(1). | Intervention |
| Ward JW, Lok AS, Thomas DL, El-Serag HB, Kim WR. Report on a single-topic conference on "Chronic viral hepatitis-strategies to improve effectiveness of screening and treatment". Hepatology. 2012;55(1):307-15. | Editorial or review |
| Watterson JM, Stallcup P, Escamilla D, Chernay P, Reyes A, Trevino SC. Evaluation of the Ortho-Clinical Diagnostics Vitros ECi Anti-HCV test: comparison with three other methods. J Clin Lab Anal. 2007;21(3):162-6. | Reference standard |
| White DA, Anderson ES, Pfeil SK, Trivedi TK, Alter HJ. Results of a Rapid Hepatitis C Virus Screening and Diagnostic Testing Program in an Urban Emergency Department. Ann Emerg Med. 2015 Jul 29. | Outcomes |
| Wiese M, Berr F, Lafrenz M, Porst H, Oesen U. Low frequency of cirrhosis in a hepatitis C (genotype 1b) single-source outbreak in germany: a 20-year multicenter study. Hepatology. 2000 Jul;32(1):91-6. | Population |
| Wilson E, Beckmann M. Antenatal screening for hepatitis C: Universal or risk factor based? Aust N Z J Obstet Gynaecol. 2015 Aug;55(4):318-22. | Population |
| Wong VW, Wong GL, Chim AM, Cheng TF, Cheung SW, Lai CM, et al. Targeted hepatitis C screening among ex-injection drug users in the community. J Gastroenterol Hepatol. 2014 Jan;29(1):116-20. | Intervention |
| Wray CM, Davis AM. Screening for hepatitis C. JAMA - Journal of the American Medical Association. 2015;313(18):1855-6. | Guideline |
| Wu FB, Ouyan HQ, Tang XY, Zhou ZX. Double-antigen sandwich time-resolved immunofluorometric assay for the detection of anti-hepatitis C virus total antibodies with improved specificity and sensitivity. J Med Microbiol. 2008;57(8):947-53. | Population |
| Wu S, Liu Y, Cheng L, Yin B, Peng J, Sun Z. Clinical evaluation of the signal-to-cutoff ratios of hepatitis C virus antibody screening tests used in China. J Med Virol. 2011 Nov;83(11):1930-7. | Intervention |
| Xia YH, Chen W, Tucker JD, Wang C, Ling L. HIV and hepatitis C virus test uptake at methadone clinics in Southern China: opportunities for expanding detection of bloodborne infections. BMC Public Health. 2013;13:899, 2013. | Outcomes |
| Xie L, Wu XD, Huang DZ, Chen HL, He LX, Wang J, et al. Clinical application and analysis of hepatitis C virus NS3 antigen detection by ELISA in human serum. Chin Med J. 2007 Feb 20;120(4):294-9. | Intervention |
| Yehia BR, Schranz AJ, Umscheid CA, Lo RI, V. The treatment cascade for chronic hepatitis C virus infection in the United States: A systematic review and meta-analysis. PLoS ONE. 2014;9(7). | Editorial or review |
| Yoo SJ, Wang LL, Ning HC, Tao CM, Hirankarn N, Kuakarn S, et al. Evaluation of the Elecsys() Anti-HCV II assay for routine hepatitis C virus screening of different Asian Pacific populations and detection of early infection. J Clin Virol. 2015 Mar;64:20-7. | Reference standard |
| Zachary P, Ullmann M, Djeddi S, Wendling MJ, Schvoerer E, Stoll-Keller F, et al. Evaluation of two commercial enzyme immunoassays for diagnosis of hepatitis C in the conditions of a virology laboratory. Pathol Biol (Paris). 2004 Nov;52(9):511-6. | Reference standard |
| Zadeh SM, Kassaian N, Ataei B, Nokhodian Z, Adibi P. Hepatitis C screening in intravenous drug users under treatment with Methadone: An action reserch study. Journal of Isfahan Medical School. 2011;28. | Not in English or French |
| Zervou EK, Boumba DS, Liaskos C, Georgiadou S, Tsianos EV, Dalekos GN. Low prevalence of HCV, HIV, and HTLV-I/II infection markers in northwestern Greece: Results of a 3-year | Reference standard |

## Table 5: List of Studies Excluded From the Systematic Review — November 2015 Database Search

| Study | Reason for Exclusion |
|---|---|
| prospective donor study (1995-1997). Eur J Intern Med. 2003;14(1):39-44. | |
| Zhang HQ, Li SB, Wang GH, Chen K, Song XG, Feng XY. Detection of hepatitis C virus core antigen for early diagnosis of hepatitis C virus infection in plasma donor in China. World J Gastroenterol. 2007;13(19):2738-42. | Population |
| Zmuda JF, Wagoneer B, Liotta L, Whiteley G. Recognition of multiple classes of hepatitis C antibodies increases detection sensitivity in oral fluid. Clin Diagn Lab Immunol. 2001;8(6):1267-70. | Reference standard |
| Zuure F, Davidovich U, Kok G, Depla AC, Hoebe C, van Den Hoek A, et al. Evaluation of a risk assessment questionnaire to assist hepatitis C screening in the general population. Euro Surveill. 2010 Apr 15;15(15):19539. | Intervention |
| Zuure FR, Bouman J, Martens M, Vanhommerig JW, Urbanus AT, Davidovich U, et al. Screening for hepatitis B and C in first-generation Egyptian migrants living in the Netherlands. Liver Int. 2013;33(5):727-38. | Comparator |
| Zuure FR, Urbanus AT, Langendam MW, Helsper CW, van den Berg CH, Davidovich U, et al. Outcomes of hepatitis C screening programs targeted at risk groups hidden in the general population: a systematic review. BMC Public Health. 2014;14:66, 2014. | Editorial or review |

## Table 6: List of Studies Excluded From the Systematic Review — May 2016 Database Search

| Study | Reason for Exclusion |
|---|---|
| Achwan WA, Muttaqin Z, Zakaria E, Depamede SA, Mulyanto, Sumoharjo S, et al. Epidemiology of hepatitis B, C, and E viruses and human immunodeficiency virus infections in Tahuna, Sangihe-Talaud Archipelago, Indonesia. Intervirology. 2007;50(6):408-11. | Population |
| Agarwal N, Chatterjee K, Coshic P, Borgohain M. Nucleic acid testing for blood banks: an experience from a tertiary care centre in New Delhi, India. Transfus Apheresis Sci. 2013 Dec;49(3):482-4. | Diagnostic test |
| Akalin S, Baskan B, Sacar S, Sayin-Kutlu S, Turgut H. Seroprevalence of HBsAg, Anti-HCV and RPR in blood donors in Denizli, Turkey. Klimik Dergisi. 2011;24(2):101-4. | Language other than English or French |
| Akkarathamrongsin S, Praianantathavorn K, Hacharoen N, Theamboonlers A, Tangkijvanich P, Poovorawan Y. Seroprevalence and genotype of hepatitis C virus among immigrant workers from Cambodia and Myanmar in Thailand. Intervirology. 2011;54(1):10-6. | Population |
| Al Dhahry SH, Nograles JC, Rajapakse SM, Al Toqi FS, Kaminski GZ. Laboratory diagnosis of viral hepatitis C: The Sultan Qaboos University Hospital experience. J Sci Res Med Sci. 2003 Aug;5(1-2):15-20. | Population |
| Albadalejo J, Alonso R, Antinozzi R, Bogard M, Bourgault AM, Colucci G, et al. Multicenter evaluation of the COBAS AMPLICOR HCV assay, an integrated PCR system for rapid detection of hepatitis C virus RNA in the diagnostic laboratory. J Clin Microbiol. 1998 Apr;36(4):862-5 | Population |
| Albertoni G, Arnoni CP, Araujo PR, Carvalho FO, Barreto JA. Signal to cut-off (S/CO) ratio and detection of HCV genotype 1 by real-time PCR one-step method: is there any direct relationship? Braz J Infect Dis. 2010 Mar;14(2):147-52. | Population |

## Table 6: List of Studies Excluded From the Systematic Review — May 2016 Database Search

| Study | Reason for Exclusion |
|---|---|
| Alborino F, Burighel A, Tiller FW, van Helden J, Gabriel C, Raineri A, et al. Multicenter evaluation of a fully automated third-generation anti-HCV antibody screening test with excellent sensitivity and specificity. Med Microbiol Immunol (Berl). 2011 May;200(2):77-83. | Outcomes |
| Allain JP, Sarkodie F, senso-Mensah K, Owusu-Ofori S. Relative safety of first-time volunteer and replacement donors in West Africa. Transfusion. 2010 Feb;50(2):340-3. | Diagnostic test |
| Allain JP, Coghlan PJ, Kenrick KG, Whitson K, Keller A, Cooper GJ, et al. Prediction of hepatitis C virus infectivity in seropositive Australian blood donors by supplemental immunoassays and detection of viral RNA. Blood. 1991 Nov 1;78(9):2462-8. | Diagnostic test |
| Allain JP, Kitchen A, Aloysius S, Reeves I, Petrik J, Barbara JA, et al. Safety and efficacy of hepatitis C virus antibody screening of blood donors with two sequential screening assays. Transfusion. 1996 May;36(5):401-5. | Screening test |
| Alzahrani AJ. Simultaneous detection of hepatitis C virus core antigen and antibodies in Saudi drug users using a novel assay. J Med Virol. 2008;80(4):603-6. | Population |
| Alzahrani AJ, Obeid OE, Al-Ali A, Imamwardi B. Detection of hepatitis C virus and human immunodeficiency virus in expatriates in Saudi Arabia by antigen-antibody combination assays. JIDC. 2009;3(3):235-8. | Population |
| Andreu J, Abad MA, Sanchez-Quijano A, Torronteras R, Luque F, Garcia de las HJ, et al. High rate of nonspecific anti-hepatitis C reactivity amongst homosexual men in comparison with that found in other sexually active groups and blood donors. Viral Hepatitis and AIDS Study Group. J Intern Med. 1994 Jul;236(1):73-7. | Diagnostic test |
| Ansaldi F, Bruzzone B, Salmaso S, Rota MC, Durando P, Gasparini R, et al. Different seroprevalence and molecular epidemiology patterns of hepatitis C virus infection in Italy. J Med Virol. 2005 Jul;76(3):327-32. | Screening test |
| Ansaldi F, Icardi G. Simultaneous detection of anti-HCV antibody and HCV core antigen. Methods Mol Biol. 2009;510:15-23. | Population |
| Aparicio T, Bonnaud G, Lucet JC, Vuagnat A, Leroy C, Bouchaud O, et al. Evaluation of three testing strategies for detection of hepatitis C in a hospital medical consultation and in an HIV testing center. Gastroenterol Clin Biol. 2001;25(5):515-20. | Population |
| Arora S, Doda V. Role of signal-to-cut-off ratios of anti-hepatitis C virus antibody by enzyme immunoassays along with ID-NAT for screening of whole blood donors in India. Asian J Transfus Sci. 2016;10(1):75-8. | Diagnostic test |
| Aspinall EJ, Doyle JS, Corson S, Hellard ME, Hunt D, Goldberg D, et al. Targeted hepatitis C antibody testing interventions: a systematic review and meta-analysis. Eur J Epidemiol. 2015 Feb;30(2):115-29. | Study design |
| Assarehzadegan MA, Boroujerdnia MG, Zandian K. Prevalence of hepatitis B and C infections and HCV genotypes among haemophilia patients in Ahvaz, Southwest Iran. Iranian Red Crescent Medical Journal. 2012;14(8):3. | Population |
| Barbosa AP, Martins RM, Teles SA, Silva SA, Oliveira JM, Yoshida CF. Prevalence of hepatitis C Virus infection among hemophiliacs in Central Brazil. Memȼrias do Instituto Oswaldo Cruz. 2002 Jul;97(5):643-4. | Population |
| Barbosa VS, Silva NA, Martins RM. Hepatitis C virus seroprevalence and genotypes in patients with diffuse connective tissue diseases and spondyloarthropathies. Braz J Med Biol Res. 2005 May;38(5):801-5. | Population |
| Baviskar BP, Chowdhary M, Mohan TK, Ghosh DK. Serological study of transfusion transmitted diseases. Pravara Medical Review. 2012;4(1):13-4. | Diagnostic test |
| Beardsley AM, LaBrooy JT, Rozen L, Gowans EJ. A comparison of hepatitis C virus (HCV)-RNA and--antibody as markers of infection and predictors of infectivity. Aust N Z J Med. 1994 Apr;24(2):182-7. | Population |

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| Study | Reason for Exclusion |
|---|---|
| Beckers EA, Thijssen PM, Nijdam T, Van Rhenen DJ. Evaluation of anti-HCV ELISA seropositivity in voluntary blood donors: a proposal for donor counseling strategies. Infusionsther Transfusionsmed. 1994 Jun;21(3):143-9. | Screening test |
| Begum Z, Lateef MA, Shaik G, Ruhi S. Prevalence of hepatitis B virus, hepatitis C virus and human immunodeficiency virus is and around Gulbarga: A hospital blood bank based 10 year study. RJPBCS. 2013;4(3):1289-95. | Diagnostic test |
| Benouda A, Boujdiya Z, Ahid S, Abouqal R, Adnaoui M. Prevalence of hepatitis C virus infection in Morocco and serological tests assessment of detection for the viremia prediction. Pathol Biol (Paris). 2009;57(5):368-72. | Diagnostic test |
| Bossi V, Galli C. Quantitative signal of anti-HCV by an automated assay predicts viremia in a population at high prevalence of hepatitis C virus infection. J Clin Virol. 2004 May;30(1):45-9. | Population |
| Bouare N, Vaira D, Gothot A, Delwaide J, Bontems S, Seidel L, et al. Prevalence of HIV and HCV infections in two populations of Malian women and serological assays performances. World J Hepatol. 2012 Dec 27;4(12):365-73. | Population |
| Bozorgi SH, Ramezani H, Nooranipour M, Ahmadi M, Baghernejad A, Mostajeri A, et al. Risk factors of viral hepatitis: yet to explore. Transfus Apheresis Sci. 2012 Oct;47(2):145-9. | Diagnostic test |
| Brandao CU, Marques BL, Marques VA, Villela-Nogueira CA, do à KMR, de Paula MT, et al. Simultaneous detection of hepatitis C virus antigen and antibodies in dried blood spots. J Clin Virol. 2013 Jun;57(2):98-102. | Diagnostic test |
| Bresee JS, Mast EE, Coleman PJ, Baron MJ, Schonberger LB, Alter MJ, et al. Hepatitis C virus infection associated with administration of intravenous immune globulin: a cohort study. JAMA. 1996;276(19):1563-7. | Population |
| Brito-Zeron P, Gheitasi H, Retamozo S, Bove A, Londono M, Sanchez-Tapias JM, et al. How hepatitis C virus modifies the immunological profile of Sjogren syndrome: analysis of 783 patients. Arthritis Res Ther. 2015;17:250. | Diagnostic test |
| Brojer E, Gronowska A, Medynska J, Grabarczyk P, Mikulska M, Letowska M, et al. The hepatitis C virus genotype and subtype frequency in hepatitis C virus RNA-positive, hepatitis C virus antibody-negative blood donors identified in the nucleic acid test screening program in Poland. Transfusion. 2004 Dec;44(12):1706-10. | Population |
| Brown AE, Ross DA, Simpson AJH, Erskine RS, Murphy G, Parry JV, et al. Prevalence of markers for HIV, hepatitis B and hepatitis C infection in UK military recruits. Epidemiol Infect. 2011;139(8):1166-71. | Diagnostic test |
| Bruhn R, Lelie N, Busch M, Kleinman S, International NAT Study Group. Relative efficacy of nucleic acid amplification testing and serologic screening in preventing hepatitis C virus transmission risk in seven international regions. Transfusion [Internet]. 2015 Jun [cited 2015 Dec 8];55(6):1195-205. | Diagnostic test |
| Caldwell SH, Li X, Rourk RM, Millar A, Sosnowski KM, Sue M, et al. Hepatitis C infection by polymerase chain reaction in alcoholics: false-positive ELISA results and the influence of infection on a clinical prognostic score. Am J Gastroenterol. 1993 Jul;88(7):1016-21. | Population |
| Candotti D, Temple J, Sarkodie F, Allain JP. Frequent recovery and broad genotype 2 diversity characterize Hepatitis C virus infection in Ghana, West Africa. J Virol. 2003;77(14):7914-23. | Diagnostic test |
| Candotti D, Sarkodie F, Allain JP. Residual risk of transfusion in Ghana. Br J Haematol. 2001;113(1):37-9. | Diagnostic test |
| Carmo RA, Oliveira GC, Guimaraes MD, Oliveira MS, Lima AA, Buzek SC, et al. Hepatitis C virus infection among Brazilian hemophiliacs: a virological, clinical and epidemiological study. Braz J Med Biol Res. 2002 May;35(5):589-98. | Population |
| Carvalhana SC, Leitao J, Alves AC, Bourbon M, Cortez-Pinto H. Hepatitis B and C | Screening test |

## Table 6: List of Studies Excluded From the Systematic Review — May 2016 Database Search

| Study | Reason for Exclusion |
|---|---|
| prevalence in Portugal: Disparity between the general population and high-risk groups. Eur J Gastroenterol Hepatol. 2016;28(6):640-4. | |
| Chandrashekar S. Half a decade of mini-pool nucleic acid testing: cost-effective way for improving blood safety in India. Asian J Transfus Sci. 2014 Jan;8(1):35-8. | Diagnostic test |
| Charlewood R, Flanagan P. Ultrio and Ultrio Plus non-discriminating reactives: false reactives or not? Vox Sang. 2013 Jan;104(1):7-11. | Diagnostic test |
| Chatterjee K, Coshic P, Borgohain M, Premchand, Thapliyal RM, Chakroborty S, et al. Individual donor nucleic acid testing for blood safety against HIV-1 and hepatitis b and c viruses in a tertiary care hospital. Natl Med J India. 2012;25(4):207-9. | Diagnostic test |
| Chiamchanya N. The prevalence of transfusion-transmissible infection in blood donors in Thammasat University Hospital between 2007-2012. J Med Assoc Thai. 2014 Oct;97(10):1055-63. | Outcomes |
| Chien NT, Dundoo G, Horani MH, Osmack P, Morley JH, Di Bisceglie AM. Seroprevalence of viral hepatitis in an older nursing home population. J Am Geriatr Soc. 1999 Sep;47(9):1110-3. | Setting |
| Chlabicz S, Bonifatiuk I, Radziwon P. Prevalence of hepatitis C virus antibodies among blood donors in north-eastern Poland. Hepatol Res. 2005;33(3):206-10. | Outcomes |
| Choudhury N, Tulsiani S, Desai P, Shah R, Mathur A, Harimoorthy V. Serial follow-up of repeat voluntary blood donors reactive for anti-HCV ELISA. Asian J Transfus Sci. 2011 Jan;5(1):26-31. | Screening test |
| Chung HT, Lee JSK, Lok ASF. Prevention of posttransfusion hepatitis B and C by screening for antibody to hepatitis C virus and antibody to HBcAg. Hepatology. 1993;18(5):1045-9. | Population |
| Claeys H, Volckaerts A, De BH, Vermylen C. Association of hepatitis C virus carrier state with the occurrence of hepatitis C virus core antibodies. J Med Virol. 1992 Apr;36(4):259-64. | Population |
| Contreras M, Barbara JA, Anderson CC, Ranasinghe E, Moore C, Brennan MT, et al. Low incidence of non-A, non-B post-transfusion hepatitis in London confirmed by hepatitis C virus serology. Lancet. 1991 Mar 30;337(8744):753-7. | Population |
| Contreras AM, Tornero-Romo CM, Toribio JG, Celis A, Orozco-Hern ndez A, Rivera PK, et al. Very low hepatitis C antibody levels predict false-positive results and avoid supplemental testing. Transfusion. 2008;48(12):2540-8. | Screening test |
| Coppola N, Alessio L, Gualdieri L, Pisaturo M, Sagnelli C, Caprio N, et al. Hepatitis B virus, hepatitis C virus and human immunodeficiency virus infection in undocumented migrants and refugees in southern Italy, january 2012 to june 2013. Eurosurveillance. 2015;20(35). | Outcomes |
| Correa da Costa LMF, Mussi ADH, Brianeze MR, Souto FJD. Hepatitis C as a risk factor for diabetes type 2: Lack of evidence in a hospital in Central-West Brazil. Braz J Infect Dis. 2008;12(1):24-6. | Outcomes |
| Cribier B, Petiau P, Keller F, Schmitt C, Vetter D, Heid E, et al. Porphyria cutanea tarda and hepatitis C viral infection. A clinical and virologic study. Arch Dermatol. 1995 Jul;131(7):801-4. | Population |
| Cribier B, Petiau P, Stoll-Keller F, Schmitt C, Vetter D, Heid E, et al. Porphyria cutanea tarda and hepatitis C virus infection. Clinical and virological study. Ann Dermatol Venereol. 1996;123(3):200-2. in French. | Other |
| Cribier BJ, Santinelli F, Schmitt C, Stoll-Keller F, Grosshans E. Chronic urticaria is not significantly associated with hepatitis C or hepatitis G infection: a case-control study. Arch Dermatol. 1999 Nov;135(11):1335-9. | Population |
| Croom HA, Richards KM, Best SJ, Francis BH, Johnson EI, Dax EM, et al. Commercial | Population |

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| Study | Reason for Exclusion |
|---|---|
| enzyme immunoassay adapted for the detection of antibodies to hepatitis C virus in dried blood spots. J Clin Virol. 2006 May;36(1):68-71. | |
| Da Silva Cardoso M, Koerner K, Kubanek B. PCR screening in the routine of blood banking of the German Red Cross blood transfusion service of Baden-Wurttemberg. Transfusion medicine and hemotherapy. 1998;25(2-3):116-20. | Screening test |
| Da Silva Cardoso M, Koerner K, Epple S, Kubanek B. Safety of blood products derived from plasma pools: the positive impact of anti-HCV screening on the quality of such products. Vox Sang. 1996;71(3):184-6. | Population |
| Da Villa G, Andjaparidze A, Cauletti M, Franco E, Roggendorf M, Sepe A, et al. Viral hepatitis in the Bhutanese population: preliminary results of a seroepidemiological investigation. Res Virol. 1997 Mar;148(2):115-7. | Diagnostic test |
| Dai CY, Yu ML, Chuang WL, Lin ZY, Chen SC, Hsieh MY, et al. Influence of hepatitis C virus on the profiles of patients with chronic hepatitis B virus infection. Journal of Gastroenterology and Hepatology (Australia). 2001;16(6):636-40. | Population |
| Dalekos GN, Zervou EK, Bouba DS, Tsianos EV. Frequency of viraemia due to hepatitis C virus among individuals with indeterminate results after RIBA-II HCV test. A preliminary study. Hellenic Journal of Gastroenterology. 1996;9(2):160-6. | Population |
| Dalgard O, Jeansson S, Skaug K, Raknerud N, Bell H. Hepatitis C in the general adult population of Oslo: prevalence and clinical spectrum. Scand J Gastroenterol. 2003 Aug;38(8):864-70. | Screening test |
| Dammacco F, Sansonno D, Cornacchiulo V, Mennuni C, Carbone R, Lauletta G, et al. Hepatitis C virus infection and mixed cryoglobulinemia: a striking association. Int J Clin Lab Res. 1993;23(1):45-9. | Population |
| Daniel HD, Grant PR, Garson JA, Tedder RS, Chandy GM, Abraham P. Quantitation of hepatitis C virus using an in-house real-time reverse transcriptase polymerase chain reaction in plasma samples. Diagn Microbiol Infect Dis. 2008 Aug;61(4):415-20. | Population |
| Davoren A, Dillon AD, Power JP, Donnellan J, Quinn JM, Willis JW, et al. Outcome of an optional HCV screening program for blood transfusion recipients in Ireland. Transfusion. 2002 Nov;42(11):1501-6. | Screening test |
| De Beenhouwer H, Verhaert H, Claeys H, Vermylen C. Confirmation of hepatitis C virus positive blood donors by immunoblotting and polymerase chain reaction. Vox Sang. 1992;63(3):198-203. | Population |
| De Cock L, Hutse V, Verhaegen E, Quoilin S, Vandenberghe H, Vranckx R. Detection of HCV antibodies in oral fluid. J Virol Methods. 2004 Dec 15;122(2):179-83. | Population |
| De Cock L, Hutse V, Vranckx R. Correlation between detection of antibodies against hepatitis C virus in oral fluid and hepatitis C virus RNA in serum. European Journal of Clinical Microbiology and Infectious Diseases. 2005;24(8):566-8. | Population |
| De Groof D, Michielsen P, Hassane A, Leyssens N, Ramon A, Pelckmans P. Seroprevalence of HCV in the general population of Niger and in patients with chronic liver diseases: comparison of different second generation tests and PCR. Bull Soc Pathol Exot. 1997;90(3):147-9. in French. | Population |
| De Rosa G, Gobbo ML, De RA, Notare R, Garofalo S, Grimaldi M, et al. High prevalence of hepatitis c virus infection in patients with B-cell lymphoproliferative disorders in Italy. Am J Hematol. 1997;55(2):77-82. | Outcomes |
| Denoyel G, van Helden J, Bauer R, Preisel-Simmons B. Performance of a new hepatitis C assay on the Bayer ADVIA Centaur© Immunoassay System. Clin Lab. 2004;50(1-2):75-82. | Screening test |
| Desenclos JC, Bourdiol-Razes M, Rolin B, Garandeau P, Ducos J, Brechot C, et al. Hepatitis C in a ward for cystic fibrosis and diabetic patients: Possible transmission by spring-loaded finger-stick devices for self-monitoring of capillary blood glucose. Infect | Screening test |

## Table 6: List of Studies Excluded From the Systematic Review — May 2016 Database Search

| Study | Reason for Exclusion |
|---|---|
| Control Hosp Epidemiol. 2001;22(11):701-7. | |
| Dong J, Wu Y, Zhu H, Li G, Lv M, Wu D, et al. A pilot study on screening blood donors with individual-donation nucleic acid testing in China. Blood Transfus. 2014 Apr;12(2):172-9. | Diagnostic test |
| Drosten C, Nippraschk T, Manegold C, Meisel H, Brixner V, Roth WK, et al. Prevalence of hepatitis B virus DNA in anti-HBc-positive/HBsAg-negative sera correlates with HCV but not HIV serostatus. J Clin Virol. 2004 Jan;29(1):59-68. | Population |
| Dubrous P, Terrier F, Gardet V, Ait-Ameur M, Hugard L. Hepatitis C virus core antigen assay: what interest in the clinical laboratory? Immuno-Analyse et Biologie Specialisee. 2005;20(6):408-13. French. | Population |
| Dufour DR, Talastas M, Fernandez MD, Harris B. Chemiluminescence assay improves specificity of hepatitis C antibody detection. Clin Chem. 2003 Jun;49(6 Pt 1):940-4. | Screening test |
| Dupond AS, Lacour JP, Lafont C, Ortonne JP. Prevalence of hepatitis C virus in oral erosive lichen. Ann Dermatol Venereol. 1998 Oct;125(10):676-8. in French. | Population |
| Ecemis T, Akcali S, Erbay DP, Sanlidag T. The threshold value of anti-HCV test in the diagnosis of HCV infection. Turkiye Klinikleri Journal of Medical Sciences. 2012;32(6):1648-52. Turkish. | Language other than English or French |
| Eiras A, Sauleda S, Planelles D, Sede¤o M, Ibarra A, Vesga MA, et al. HCV screening in blood donations using RT-PCR in mini-pool: the experience in Spain after routine use for 2 years. Transfusion. 2003 Jun;43(6):713-20. | Screening test |
| Engels EA, Chatterjee N, Cerhan JR, Davis S, Cozen W, Severson RK, et al. Hepatitis C virus infection and non-Hodgkin lymphoma: results of the NCI-SEER multi-center case-control study. Int J Cancer. 2004 Aug 10;111(1):76-80. | Population |
| Ergunay K, Sener B, Alp A, Karakaya J, Hascelik G. Utility of a commercial quantitative hepatitis C virus core antigen assay in a diagnostic laboratory setting. Diagn Microbiol Infect Dis. 2011 Aug;70(4):486-91. | Population |
| Fang CT, Field SP, Busch MP, Heyns AP. Human immunodeficiency virus-1 and hepatitis C virus RNA among South African blood donors: estimation of residual transfusion risk and yield of nucleic acid testing. Vox Sang. 2003 Jul;85(1):9-19. | Diagnostic test |
| Farshadpour F, Makvandi M, Samarbafzadeh AR, Jalalifar MA. Determination of hepatitis C virus genotypes among blood donors in Ahvaz, Iran. Indian Journal of Medical Microbiology. 2010;28(1):54-6. | Screening test |
| Feng S, Wei B, Liu Q, Wang T, Li D, Rao C, et al. Evaluation of a novel HISCL chemiluminescence enzyme immunoassay for laboratory screening of hepatitis C virus. Clin Vaccine Immunol. 2016 May 11. | Population |
| Ferreira MR, Lonardoni MV, Bertolini DA. Hepatitis C: Serological and molecular diagnosis and genotype in haemophilic patients at the Regional Hemocenter of Maringa, Maringa PR Brazil. Haemophilia. 2008;14(4):810-5. | Population |
| Ferri C, Baicchi U, la CL, Greco F, Longombardo G, Mazzoni A, et al. Hepatitis C virus-related autoimmunity in patients with porphyria cutanea tarda. Eur J Clin Invest. 1993 Dec;23(12):851-5. | Population |
| Fierz W. Serologic testing for HBsAg, hepatitis C and HIV 1 and 2 using the COBAS core II immunochemistry analyser. Clin Lab. 1997;43(3):147-52. | Population |
| Fonseca BPF, Marques CFS, Nascimento LD, Mello MB, Silva LBR, Rubim NM, et al. Development of a multiplex bead-based assay for detection of hepatitis C virus. Clinical and Vaccine Immunology. 2011;18(5):802-6. | Population |
| Rotermann M, Langlois K, Andonov A, Trubnikov M. Seroprevalence of hepatitis B and C virus infections: Results from the 2007 to 2009 and 2009 to 2011 Canadian Health Measures Survey. Health Rep. 2016 Mar 16;24(11). Publication no. 82-003-x. | Population |

## Table 6: List of Studies Excluded From the Systematic Review — May 2016 Database Search

| Study | Reason for Exclusion |
|---|---|
| Fretz C, Jeannel D, Stuyver L, Herve V, Lunel F, Boudifa A, et al. HCV infection in a rural population of the Central African Republic (CAR): evidence for three additional subtypes of genotype 4. J Med Virol. 1995;47(4):435-7. | Screening test |
| Galel SA, Strong DM, Tegtmeier GE, Holland PV, Kuramoto IK, Kemper M, et al. Comparative yield of HCV RNA testing in blood donors screened by 2.0 versus 3.0 antibody assays. Transfusion. 2002 Nov;42(11):1507-13. | Population |
| Garson JA, Tedder RS, Briggs M, Tuke P, Glazebrook JA, Trute A, et al. Detection of hepatitis C viral sequences in blood donations by "nested" polymerase chain reaction and prediction of infectivity. Lancet. 1990 Jun 16;335(8703):1419-22. | Population |
| Garson JA, Clewley JP, Simmonds P, Zhang LQ, Mori J, Ring C, et al. Hepatitis C viraemia in United Kingdom blood donors. A multicentre study. Vox Sang. 1992;62(4):218-23. | Screening test |
| Gerayli S, Meshkat Z, Pasdar A, Mozafari PM, Banihashemi E, Khajavi MA, et al. The association between oral lichen planus and hepatitis C virus infection; a report from northeast of Iran. Jundishapur Journal of Microbiology. 2015;8(4). | Population |
| Gessoni G, Manoni F, Dolci L, Valverde S, Antico F, Piacentini I. Relevance of anti-HCV antibody (IgG and IgM) and HCV-RNA in diagnosis of HCV infection. Alpe Adria Microbiology Journal. 1997;6(1-2):35-43. | Population |
| Giannoulis E, Economopoulos T, Mandraveli K, Giannoulis K, Nikolaides C, Zervou E, et al. The prevalence of hepatitis C and hepatitis G virus infection in patients with B cell non-Hodgkin lymphomas in Greece: a Hellenic Cooperative Oncology Group Study. Acta Haematol. 2004;112(4):189-93. | Population |
| Gibney KB, Torresi J, Lemoh C, Biggs BA. Isolated core antibody hepatitis B in sub-Saharan African immigrants. J Med Virol. 2008 Sep;80(9):1565-9. | Population |
| Gisbert JP, Garcia-Buey L, Alonso A, Rubio S, Hernandez A, Pajares JM, et al. Hepatocellular carcinoma risk in patients with porphyria cutanea tarda. Eur J Gastroenterol Hepatol. 2004;16(7):689-92. | Screening test |
| Glikberg F, Brawer-Ostrovsky J, Ackerman Z. Very high prevalence of hepatitis B and C in Bukharian Jewish immigrants to Israel. J Clin Gastroenterol. 1997 Jan;24(1):30-3. | Diagnostic test |
| Gon‡ales NS, Costa FF, Vassallo J, Gon‡ales FL. Diagnosis of hepatitis C virus in Brazilian blood donors using a reverse transcriptase nested polymerase chain reaction: comparison with enzyme immunoassay and recombinant protein immunoblot assay. Revista do Instituto de Medicina Tropical de Sao Paulo. 2000;42(5):263-7. | Population |
| Gong S, Schmotzer CL, Zhou L. Evaluation of quantitative real-time PCR as a hepatitis C virus supplementary test after RIBA discontinuation. J Clin Lab Anal. 2015 Oct 26. | Population |
| Gonz lez A, Esteban JI, Madoz P, Viladomiu L, Genesca J, Mu¤iz E, et al. Efficacy of screening donors for antibodies to the hepatitis C virus to prevent transfusion-associated hepatitis: final report of a prospective trial. Hepatology. 1995 Aug;22(2):439-45. | Screening test |
| Gonzalez HC, Lamerato L, Rogers CG, Gordon SC. Chronic hepatitis C infection as a risk factor for renal cell carcinoma. Dig Dis Sci. 2015;60(6):1820-4. | Population |
| Gonzalez-Perez I, Gonz lez Gonz lez YJ, Vina-Rodriguez A, rmas Cayarga A, Sol¡s RL. The usefulness of Umelosa hepatitis C virus qualitative kit as supplemental test for confirmation of hepatitis C virus infection. Rev Soc Bras Med Trop. 2004 Jan;37(1):25-7. | Population |
| Grabarczyk P, Kopacz A, Sulkowska E, Kubicka-Russel D, Mikulska M, Brojer E, et al. Blood donors screening for blood born viruses in Poland. Przegl Epidemiol. 2015;69(3):473-7. | Screening test |
| Groom H, Dieperink E, Nelson DB, Garrard J, Johnson JR, Ewing SL, et al. Outcomes of a hepatitis C screening program at a large urban VA medical center. J Clin Gastroenterol. 2008 Jan;42(1):97-106. | Population |

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| Study | Reason for Exclusion |
|---|---|
| Gu S, Liu J, Zhang H, Gu B, Lai H, Zhou H, et al. Core antigen tests for hepatitis C virus: a meta-analysis. Mol Biol Rep. 2012 Aug;39(8):8197-208. | Publication type |
| Guennoc X, Narbonne V, Jousse-Joulin S, vauchelle-Pensec V, Dougados M, Daures JP, et al. Is screening for hepatitis B and hepatitis C useful in patients with recent-onset polyarthritis? The ESPOIR cohort study. J Rheumatol. 2009 Jul;36(7):1407-13. | Diagnostic test |
| Gultepe B, Dulger AC, Aytemiz E. Epidemiology of the hepatitis C infection in Van's region. Eastern Journal of Medicine. 2013;18(3):123-6. | Population |
| Halawani M. Hepatitis C virus genotypes among patients with lichen planus in the Kingdom of Saudi Arabia. Int J Dermatol. 2014 Feb;53(2):171-7. | Population |
| Halawani M. Screening of hepatitis C virus genotypes in urticaria patients in Saudi Arabia. Genet Test Mol Biomarkers. 2012 Aug;16(8):964-7. | Population |
| Halawani M, Balbisi A, Alotaibi H, Alsaif F, Bakir TM. The prevalence of HCV antibodies in skin disease patients in Saudi Arabia. Saudi Pharmaceutical Journal. 2010;18(1):35-9. | Population |
| Hartleb M, Gutkowski K, Zejda JE, Chudek J, Wiecek A. Serological prevalence of hepatitis B virus and hepatitis C virus infection in the elderly population: Polish nationwide survey--PolSenior. Eur J Gastroenterol Hepatol. 2012 Nov;24(11):1288-95. | Diagnostic test |
| Hayashi J, Kishihara Y, Yamaji K, Yoshimura E, Kawakami Y, Akazawa K, et al. Transmission of hepatitis C virus by health care workers in a rural area of Japan. Am J Gastroenterol. 1995 May;90(5):794-9. | Population |
| Heck E, Brown A, Cavanagh HD. Nucleic acid testing and tissue safety: an eye bank's five-year review of HIV and hepatitis testing for donor corneas. Cornea. 2013 Apr;32(4):503-5. | Population |
| Henrard DR, Berthillon P, Scheffel JW, Ladaique PL, Moore BS, Pailhous MC, et al. Lack of evidence of hepatitis C infection in 290 blood component recipients, demonstrated by several single-antigen research immunoassays. Transfusion. 1998;38(2):194-8. | Population |
| Hitzler WE, Runkel S. Screening of blood donations by hepatitis C virus polymerase chain reaction (HCV-PCR) improves safety of blood products by window period reduction. Clin Lab. 2001;47(5-6):219-22. | Outcomes |
| Hitzler WE, Runkel S. Routine HCV PCR screening of blood donations to identify early HCV infection in blood donors lacking antibodies to HCV. Transfusion. 2001 Mar;41(3):333-7. | Screening test |
| Huang WS, Lu SN, Wang JH, Lee CM, Tung HD, Chen TM, et al. Prediction of viremia for cases of hepatitis C virus (HCV) infection using a third-generation anti-HCV enzyme immunoassay test. Hepatogastroenterology. 2005 May;52(63):893-6. | Population |
| Hwang JP, Mohseni M, Gor BJ, Wen S, Guerrero H, Vierling JM. Hepatitis B and hepatitis C prevalence and treatment referral among Asian Americans undergoing community-based hepatitis screening. Am J Public Health. 2010 Apr 1;100 Suppl 1:S118-S124. | Population |
| Hyland C, Seed CR, Kiely P, Parker S, Cowley N, Bolton W. Follow-up of six blood donors highlights the complementary role and limitations of hepatitis C virus antibody and nucleic acid amplification tests. Vox Sang. 2003 Jul;85(1):1-8. | Diagnostic test |
| Icardi G, Bruzzone B, Gota F, Torre F, Giannini E, Massone L, et al. A new assay for hepatitis C virus (HCV) core antigen detection: an alternative to nucleic acid technologies in positive or indeterminate anti-HCV subjects? Ann Ig (Roma). 2003 Nov;15(6):863-70. | Population |
| Irshad M, Ansari MA, Irshad K, Lingaiah R. Novel single-step multiplex real-time polymerase chain reaction assay for simultaneous quantification of hepatitis virus A, B, C, and E in serum. J Gastroenterol Hepatol. 2013 Dec;28(12):1869-76. | Population |
| Isikdogan A, Ayyildiz O, Dursun M, Tiftik N, Batun S, Muftuoglu E. Hepatitis C virus in patients with non-Hodgkin's lymphoma in southeastern Anatolia region of Turkey: a prospective case-control study of 119 patients. Leuk Lymphoma. 2003 Oct;44(10):1745-7. | Population |

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| Study | Reason for Exclusion |
|---|---|
| Jain R, Aggarwal P, Gupta GN. Need for nucleic acid testing in countries with high prevalence of transfusion-transmitted infections. ISRN Gastroenterology. 2012;2012: 718671. | Diagnostic test |
| Janot C. ELISA kits for detection of anti-HCV antibodies. "Viral Hepatitis" Working Group of the French Society of Blood Transfusion. Transfus Clin Biol. 1994;1(1):47-8. | Outcomes |
| Janot C, Courouce AM, Barin F, Lunel-Fabiani F, Trepo C, Botte C. Screening tests of anti-HVC antibodies used in France. Analysis of sensitivity. Transfus Clin Biol. 1994;1(4):295-301. in French. | Population |
| Jeannel D, Fretz C, Traore Y, Kohdjo N, Bigot A, Gamy EP, et al. Evidence for high genetic diversity and long-term endemicity of hepatitis C virus genotypes 1 and 2 in West Africa. J Med Virol. 1998;55(2):92-7. | Screening test |
| Jonas G, Pelzer C, Beckert C, Hausmann M, Kapprell HP. Performance characteristics of the ARCHITECT© anti-HCV assay. J Clin Virol. 2005 Oct;34(2):97-103. | Diagnostic test |
| Kania D, Sangare L, Sakande J, Koanda A, Nebie YK, Zerbo O, et al. A new strategy to improve the cost-effectiveness of human immunodeficiency virus, hepatitis B virus, hepatitis C virus, and syphilis testing of blood donations in sub-Saharan Africa: A pilot study in Burkina Faso. Transfusion. 2009;49(10):2237-40. | Diagnostic test |
| Kant J, Kratzsch J, Maier M, Liebert UG, Berg T, Wiegand J. HBsAg and anti-HCV screening in elderly hospitalized patients of a German tertiary referral centre. Z Gastroenterol. 2016;54(3):231-7. | Setting |
| Kapeluto JE, Kadatz M, Wormsbecker A, Sidhu K, Yoshida EM. Screening, detecting and enhancing the yield of previously undiagnosed hepatitis B and C in patients with acute medical admissions to hospital: A pilot project undertaken at the Vancouver General Hospital. Canadian Journal of Gastroenterology and Hepatology. 2014;28(6):315-8. A | Diagnostic test |
| Karavelioglu D, Koytak ES, Bozkaya H, Uzunalimoglu O, Bozdayi AM, Yurdaydin C. Lichen planus and HCV infection in Turkish patients. Turk J Gastroenterol. 2004 Sep;15(3):133-6 | Population |
| Keiserman DR, Both CT, Mattos AA, Remiao J, Alexandre CO, Sherman KE. Intrafamilial transmission of hepatitis C virus in patients with hepatitis C and human immunodeficiency virus coinfection. Am J Gastroenterol. 2003 Apr;98(4):878-83. | Population |
| Kessler HH, Santner B, Umlauft F, Urbanek M, Kronawetter M, Pierer K, et al. Detection of hepatitis C viral sequences in serum by 'nested' polymerase chain reaction (PCR) and a commercial single-round PCR assay. Clinical and Diagnostic Virology. 1995;4(3):239-50. | Population |
| Khaja MN, Madhavi C, Thippavazzula R, Nafeesa F, Habib AM, Habibullah CM, et al. High prevalence of hepatitis C virus infection and genotype distribution among general population, blood donors and risk groups. Infect Genet Evol. 2006 May;6(3):198-204. | Outcomes |
| Kim S, Kim JH, Yoon S, Park YH, Kim HS. Clinical performance evaluation of four automated chemiluminescence immunoassays for hepatitis C virus antibody detection. J Clin Microbiol. 2008 Dec;46(12):3919-23. | Population |
| Klanrit P, Thongprasom K, Rojanawatsirivej S, Theamboonlers A, Poovorawan Y. Hepatitis C virus infection in Thai patients with oral lichen planus. Oral Dis. 2003 Nov;9(6):292-7. | Population |
| Kleinman S, Alter H, Busch M, Holland P, Tegtmeier G, Nelles M, et al. Increased detection of hepatitis C virus (HCV)-infected blood donors by a multiple-antigen HCV enzyme immunoassay. Transfusion. 1992 Nov;32(9):805-13. | Screening test |
| Komatsu F, Takasaki K. Determination of serum hepatitis C virus (HCV) core protein using a novel approach for quantitative evaluation of HCV viraemia in anti-HCV-positive patients. Liver. 1999;19(5):375-80. | Population |
| Kosan E, Kocazeybek B, Altunay H, Aymelek M, Alan E, Saribas S, et al. Can the nucleic acid amplification test (NAT) be an alternative to the serologic tests? A prospective study, the results of 18,200 blood donors from the Turkish Red Crescent. Transfus Apheresis Sci. | Diagnostic test |

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| Study | Reason for Exclusion |
|---|---|
| 2010 Dec;43(3):269-72. | |
| Kumar R, Gupta S, Kaur A, Gupta M. Individual donor-nucleic acid testing for human immunodeficiency virus-1, hepatitis C virus and hepatitis B virus and its role in blood safety. Asian J Transfus Sci [Internet]. 2015 Jul [cited 2015 Dec 10];9(2):199-202. | Diagnostic test |
| Kuo YH, Chang KC, Wang JH, Tsai PS, Hung SF, Hung CH, et al. Is hepatitis C virus core antigen an adequate marker for community screening? J Clin Microbiol. 2012 Jun;50(6):1989-93. | Population |
| Kurtz JB, Boxall E, Qusir N, Shirley J, Coleman D, Chandler C. The diagnostic significance of an assay for 'total' hepatitis C core antigen. J Virol Methods. 2001 Aug;96(2):127-32. | Population |
| Lai KK, Jin M, Yuan S, Larson MF, Dominitz JA, Bankson DD. Improved reflexive testing algorithm for hepatitis C infection using signal-to-cutoff ratios of a hepatitis C virus antibody assay. Clin Chem. 2011 Jul;57(7):1050-6. | Diagnostic test |
| Lai ME, Mazzoleni AP, Farci P, Melis A, Porru A, Orgiana G, et al. Markers of hepatitis C virus infection in Sardinian blood donors: relationship with alanine aminotransferase levels. J Med Virol. 1993;41(4):282-8. | Screening test |
| Lambert N. Value of HCV antigen-antibody combined HCV assay in hepatitis C diagnosis. Dev Biol (Basel). 2007;127:113-21. | Publication type |
| Langar H, Triki H, Gouider E, Bahri O, Djebbi A, Sadraoui A, et al. Blood-transmitted viral infections among haemophiliacs in Tunisia. Transfus Clin Biol. 2005;12(4):301-5. in French. | Screening test |
| Lashari AA, Bhatti K, Mahar T, Hafeez R. Frequency of hepatitis C in general surgical patients at Teaching Hospital Khairpur Sindh. Med Forum Mon. 2014;25(4):7-9. | Other |
| Lavanchy D, Mayerat C, Morel B, Schneider P, Zufferey C, Gonvers JJ, et al. Evaluation of third-generation assays for detection of anti-hepatitis C virus (HCV) antibodies and comparison with presence of HCV RNA in blood donors reactive to c100-3 antigen. J Clin Microbiol. 1994 Sep;32(9):2272-5. | Screening test |
| Lee CE, Sri PS, Syed Omar SF, Mahadeva S, Ong LY, Kamarulzaman A. Evaluation of the dried blood spot (DBS) collection method as a tool for detection of HIV Ag/Ab, HBsAg, anti-HBs and anti-HCV in a Malaysian tertiary referral hospital. Ann Acad Med Singapore. 2011 Oct;40(10):448-53. | Population |
| Lee SR, Wood CL, Lane MJ, Francis B, Gust C, Higgs CM, et al. Increased detection of hepatitis C virus infection in commercial plasma donors by a third-generation screening assay. Transfusion. 1995 Oct;35(10):845-9. | Outcomes |
| Lee HM, Naor J, Alhindi R, Chinfook T, Krajden M, Mazzulli T, et al. Detection of hepatitis C virus in the corneas of seropositive donors. Cornea. 2001;20(1):37-40. | Population |
| Levi JE, Wendel S, Takaoka DT, Silva IC, Castro JP, Torezan-Filho MA, et al. Replacement of HIV p24 Ag test by a multiplex RT-PCR method for primary screening of blood donors. Rev Inst Med Trop Sao Paulo. 2007 May;49(3):171-6. | Diagnostic test |
| Li D, Zhu S, Wang T, An J, Wang L, Tao C. Comparison of elecsys anti-HCV II assay with other HCV screening assays. J Clin Lab Anal. 2015 Dec 14. | Population |
| Lieshout-Krikke RW, Zaaijer HL, Van De Laar TJW. Predonation screening of candidate donors and prevention of window period donations. Transfusion. 2015;55(2):373-8. | Outcomes |
| Linas BP, Hu H, Barter DM, Horberg M. Hepatitis C screening trends in a large integrated health system. Am J Med. 2014;127(5):398-405. | Outcomes |
| Lopez RA, Romero-Estrella S, Infante-Ramirez L, Mendez-Aquino JS, Berron-Ruiz P, Morales-Alfaro NA, et al. Hepatitis C seroprevalence in accepted versus deferred blood-donor candidates evaluated by medical history and self-exclusion form. Transfusion. 2004 | Diagnostic test |

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| Study | Reason for Exclusion |
|---|---|
| Sep;44(9):1344-9. | |
| Lozano ML, Candela MJ, Cano H, Zuazu I, Vicente V. Detection of free hepatitis C virus core antigen by enzyme-linked immunosorbent assay is not suitable for screening of granulocyte colony-stimulating factor-mobilized hematopoietic progenitor donors. Transfusion. 2004 Dec;44(12):1755-61. | Diagnostic test |
| Lucidarme D, Decoster A, Delamare C, Schmitt C, Kozlowski D, Harbonnier J, et al. An inter-laboratory study of anti-HCV antibody detection in saliva samples. Gastroenterol Clin Biol. 2003 Feb;27(2):159-62. | Population |
| Luo KX, Liang ZS, Yang SC, Zhou R, Meng QH, Zhu YW, et al. Etiological investigation of acute post-transfusion non-A, non-B hepatitis in China. J Med Virol. 1993 Mar;39(3):219-23. | Population |
| Maasoumy B, Bremer B, Raupach R, Lehmann P, Manns MP, Cornberg M, et al. How to interpret borderline HCV antibody test results: a comparative study investigating four different anti-HCV assays. Viral Immunol. 2014 Feb;27(1):7-13. | Population |
| Machain-Williams C, Talavera-Aguilar L, Cetina-Trejo RC, Carrillo-Navarrete J, Rivero-Cardenas N, Salazar MI, et al. Detection of hepatitis C virus coinfection in patients with dengue diagnosis. BioMed Research International. 2014;2014. | Screening test |
| Maity S, Nandi S, Biswas S, Sadhukhan SK, Saha MK. Performance and diagnostic usefulness of commercially available enzyme linked immunosorbent assay and rapid kits for detection of HIV, HBV and HCV in India. Virology Journal. 2012;9:290. | Population |
| Makroo RN, Arora JS, Chowdhry M, Bhatia A, Thakur UK, Minimol A. Red cell alloimmunization and infectious marker status (human immunodeficiency virus, hepatitis B virus and hepatitis C virus) in multiply transfused thalassemia patients of North India. Indian J Pathol Microbiol. 2013 Oct;56(4):378-83. | Population |
| Makroo RN, Choudhury N, Jagannathan L, Parihar-Malhotra M, Raina V, Chaudhary RK, et al. Multicenter evaluation of individual donor nucleic acid testing (NAT) for simultaneous detection of Human immunodeficiency virus -1 & hepatitis B & C viruses in Indian blood donors. Indian J Med Res. 2008;127(2):140-7. | Diagnostic test |
| Marques BL, Brandao CU, Silva EF, Marques VA, Villela-Nogueira CA, do à KM, et al. Dried blood spot samples: optimization of commercial EIAs for hepatitis C antibody detection and stability under different storage conditions. J Med Virol. 2012 Oct;84(10):1600-7. | Population |
| Maugat S, Astagneau P, Thibault V, Desruennes E, Baffoy N, Desenclos JC, et al. Nosocomial risk factors of hepatitis C infection. A multicenter study in a hospital-based population. Rev Epidemiol Sante Publique. 2003 Jun;51(3):301-8. | Setting |
| Mauser-Bunschoten EP, Bresters D, van Drimmelen AA, Roosendaal G, Cuypers HT, Reesink HW, et al. Hepatitis C infection and viremia in Dutch hemophilia patients. J Med Virol. 1995 Mar;45(3):241-6. | Population |
| Medici MC, Galli C, Calderaro A. Hepatitis C virus screening to reveal a better picture of infection. Trends in Microbiology. 2015;23(6):324-6. | Publication type |
| Medici MC, Furlini G, Rodella A, Fuertes A, Monachetti A, Calderaro A, et al. Hepatitis C virus core antigen: Analytical performances, correlation with viremia and potential applications of a quantitative, automated immunoassay. J Clin Virol. 2011;51(4):260-5. | Population |
| Medici MC, Chezzi C, Conto FD, Ferraglia F, Pinardi F, Arcangeletti MC, et al. Evolving strategy for HCV testing in an Italian tertiary care hospital. J Clin Virol. 2016;77:92-8. | Population |
| Meffre C, Larsen C, Perin A, Bouraoui L, Delarocque AE. Surveillance of screening for hepatitis C through the laboratory network RENA-VHC, France, 2000-2001. Euro Surveill. 2003 May;8(5):101-7. | Screening test |

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| Study | Reason for Exclusion |
|---|---|
| Meffre C, Le SY, arocque-Astagneau E, Dubois F, Antona D, Lemasson JM, et al. Prevalence of hepatitis B and hepatitis C virus infections in France in 2004: social factors are important predictors after adjusting for known risk factors. J Med Virol. 2010 Apr;82(4):546-55. | Screening test |
| Mejri S, Salah AB, Triki H, Alaya NB, Djebbi A, Dellagi K. Contrasting patterns of hepatitis C virus infection in two regions from Tunisia. J Med Virol. 2005 Jun;76(2):185-93. | Screening test |
| Mine H, Emura H, Miyamoto M, Tomono T, Minegishi K, Murokawa H, et al. High throughput screening of 16 million serologically negative blood donors for hepatitis B virus, hepatitis C virus and human immunodeficiency virus type-1 by nucleic acid amplification testing with specific and sensitive multiplex reagent in Japan. Journal of Virological Methods. 2003;112(1-2):145-51. | Screening test |
| Minello A, Boschi F, Harb M, Milan C, Faivre J, Hillon P. Creation of a viral hepatitis B and C registry in Cote-d'Or. Methodology, initial results. Gastroenterol Clin Biol. 1998;22(10):766-71. | Screening test |
| Minuk GY, Lerner B, Gibson SB, Johnston JB, Uhanova J, Andonov A, et al. Hepatitis B and hepatitis C viral infections in patients with chronic lymphocytic leukemia. Can J Gastroenterol Hepatol. 2014 Mar;28(3):131-4. | Population |
| Mirzaee M, Yaghobi R, Ramzi M, Nia MR. The prevalence of molecular and immunologic infective markers of hepatitis viruses in patients with hematological malignancies. Molecular Biology Reports. 2012;39(2):1217-23. | Population |
| Mison LM, Young IF, O'Donoghue M, Cowley N, Thorlton N, Hyland CA. Prevalence of hepatitis C virus and genotype distribution in an Australian volunteer blood donor population. Transfusion. 1997;37(1):73-8. | Diagnostic test |
| Mizuki N, Inoko H, Ando H, Kiyosawa K, Seki T, Geng Z, et al. Seroepidemiological studies on Silk Road ethnic groups. Tokai J Exp Clin Med. 1996 Oct;21(3):117-20. | Diagnostic test |
| Mohammadali F, Pourfathollah AA. Changes in frequency of HBV, HCV, HIV and syphilis infections among blood donors in Tehran province 2005 - 2011. Arch Iran Med. 2014 Sep;17(9):613-20. | Diagnostic test |
| Moretti M, Pieretti B, Masucci A, Sisti D, Rocchi M, Delprete E. Role of signal-to-cutoff ratios in hepatitis C virus antibody detection. Clinical and Vaccine Immunology. 2012;19(8):1329-31. | Population |
| Morton LM, Engels EA, Holford TR, Leaderer B, Zhang Y, Zahm SH, et al. Hepatitis C virus and risk of non-Hodgkin lymphoma: a population-based case-control study among Connecticut women. Cancer Epidemiol Biomarkers Prev. 2004 Mar;13(3):425-30. | Outcomes |
| Mowla K, Hajiani E. Prevalence of hepatitis C virus infection in patients with systemic lupus erythematosus: A case-control study. Hepatitis Monthly. 2008;8(1):41-4. | Population |
| Mullis CE, Laeyendecker O, Reynolds SJ, Ocama P, Quinn J, Boaz I, et al. High frequency of false-positive hepatitis C virus enzyme-linked immunosorbent assay in Rakai, Uganda. Clin Infect Dis. 2013;57(12):1747-50. | Population |
| Mulyanto, Suwignyo S, Tsauri S, Itoh K, Mizui M, Tsuda F, et al. An easy dipstick assay for anti-core antibodies to screen blood donors for hepatitis C virus viremia. Vox Sang. 1996;70(4):229-31. | Screening test |
| Munoz-Gomez R, Garc¡a-Monz¢n C, Garc¡a-Buey L, Lo IO, Borque MJ, Gar¡a-S nchez A, et al. Hepatitis C virus infection in Spanish volunteer blood donors: HCV RNA analysis and liver disease. Eur J Gastroenterol Hepatol. 1996 Mar;8(3):273-7. | Diagnostic test |
| Nadol P, O'Connor S, Duong H, Mixson-Hayden T, Tram TH, Xia GL, et al. High hepatitis C virus (HCV) prevalence among men who have sex with men (MSM) in Vietnam and associated risk factors: 2010 Vietnam Integrated Behavioural and Biologic Cross-Sectional Survey. Sex Transm Infect. 2016 Apr 4. | Population |

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| Study | Reason for Exclusion |
|---|---|
| Nakata S, Song P, Duc DD, Nguyen XQ, Murata K, Tsuda F, et al. Hepatitis C and B virus infections in populations at low or high risk in Ho Chi Minh and Hanoi, Vietnam. J Gastroenterol Hepatol. 1994 Jul;9(4):416-9. | Population |
| Nemecek V, Toulcova A, Summerova M, Koning J, Turek P. Screening and confirmation of blood donors at the Czech Republic. Transfuze a hematologie dnes. 2001;7(1):19-23. | Other |
| Nieters A, Kallinowski B, Brennan P, Ott M, Maynadie M, Benavente Y, et al. Hepatitis C and risk of lymphoma: results of the European multicenter case-control study EPILYMPH. Gastroenterology. 2006 Dec;131(6):1879-86. | Population |
| Nimboor K, Sujatha R, Golia S, Bhakthavatchalam. A study of seroprevalence of hepatitis B surface antigen, antibodies to hepatitis C virus and human immunodeficiency virus in patients visiting tertiary care centre in Bangalore. Indian Journal of Public Health Research and Development. 2014;5(4):86-9. | Screening test |
| Niu J, Kumar U, Pan Y, Liu Y, Zhan Q, Thomas H, et al. Hepatitis C virus Type I(1a) in Northern China. J Med Virol. 1995;46(1):56-60. | Population |
| Nogueira CA, Edelman DC, Nogueira CM, Nogueira SA, Coelho HS, Abrahao LJ, et al. Hepatitis C virus transfusion-transmitted infection in Brazilian cardiac surgery patients. Clin Lab. 2002;48(9-10):529-33. | Outcomes |
| Nooredinvand HA, Connell DW, Asgheddi M, Abdullah M, O'Donoghue M, Campbell L, et al. Viral hepatitis prevalence in patients with active and latent tuberculosis. World J Gastroenterol. 2015;21(29):8974-80. | Population |
| Novack L, Shinar E, Safi J, Soliman H, Yaari A, Galai N, et al. Evaluation of pooled screening for anti-HCV in two blood services set-ups. Trop Med Int Health. 2007 Mar;12(3):415-21. | Diagnostic test |
| O'Connell S, Lillis D, Cotter A, O'Dea S, Tuite H, Fleming C, et al. Opt-out panel testing for HIV, hepatitis B and hepatitis C in an urban emergency department: A pilot study. PLoS ONE. 2016;11(3). | Screening test |
| Oguz A, Aykas F, Unal D, Karahan S, Uslu E, Basak M, et al. Hepatitis B and C seroprevalence in solid tumors - necessity for screening during chemotherapy. Asian Pac J Cancer Prev. 2014;15(3):1411-4. | Screening test |
| Ohishi W, Fujiwara S, Suzuki G, Kishi T, Sora M, Matsuura S, et al. Feasibility of freeze-dried sera for serological and molecular biological detection of hepatitis B and C viruses. J Clin Microbiol. 2006 Dec;44(12):4593-5. | Population |
| Ohkawa K, Hayashi N, Yuki N, Hagiwara H, Kato M, Yamamoto K, et al. Hepatitis C virus antibody and hepatitis C virus replication in chronic hepatitis B patients. J Hepatol. 1994 Oct;21(4):509-14. | Population |
| Okayama A, Stuver SO, Tabor E, Tachibana N, Kohara M, Mueller NE, et al. Incident hepatitis C virus infection in a community-based population in Japan. J Viral Hepat. 2002 Jan;9(1):43-51. | Screening test |
| Oner S, Yapici G, Sasmaz CT, Kurt AO, Bugdayci R. Hepatitis B, hepatitis C, HIV, and VDRL seroprevalence of blood donors in Mersin, Turkey. Turk J Med Sci. 2011;41(2):335-41. | Screening test |
| Operskalski EA, Mosley JW, Tobler LH, Fiebig EW, Nowicki MJ, Mimms LT, et al. HCV viral load in anti-HCV-reactive donors and infectivity for their recipients. Transfusion. 2003;43(10):1433-41. | Population |
| Ornopia GL, Kuramoto K. Detection of anti-hepatitis C virus using chemiluminescence. J Viral Hepat. 1995;2(4):215-9. | Diagnostic test |
| Palacios A, Taylor L, Haue L, Luftig RB, Visona KA. Development of low cost peptide-based anti-hepatitis C virus screening and confirmatory assays: comparison with commercially available tests. J Med Virol. 1999 Jul;58(3):221-6. | Outcomes |

## Table 6: List of Studies Excluded From the Systematic Review — May 2016 Database Search

| Study | Reason for Exclusion |
|---|---|
| Pallavi P, Ganesh CK, Jayashree K, Manjunath GV. Seroprevalence and trends in transfusion transmitted infections among blood donors in a University Hospital blood bank: A 5 year study. Indian Journal of Hematology and Blood Transfusion. 2011;27(1):1-6. | Diagnostic test |
| Panigrahi AK, Panda SK, Dixit RK, Rao KV, Acharya SK, Dasarathy S, et al. Magnitude of hepatitis C virus infection in India: prevalence in healthy blood donors, acute and chronic liver diseases. J Med Virol. 1997 Mar;51(3):167-74. | Screening test |
| Papatheodoridis G, Sypsa V, Kantzanou M, Nikolakopoulos I, Hatzakis A. Estimating the treatment cascade of chronic hepatitis B and C in Greece using a telephone survey. J Viral Hepat. 2015 Apr;22(4):409-15. | Screening test |
| Passos EP, Silveira TR, Salazar CC, Facin AC, Souza CA, Guerin YL, et al. Hepatitis C virus infection and assisted reproduction. Hum Reprod. 2002 Aug;17(8):2085-8. | Diagnostic test |
| Pathak S, Chandrashekhar M. Transfusion transmittable infections - Seroprevalence among blood donors in a tertiary care hospital of Delhi. Asian J Transfus Sci. 2013 Jul;7(2):116-8. | Outcomes |
| Pawlotsky JM, Lonjon I, Hezode C, Raynard B, Darthuy F, Remire J, et al. What strategy should be used for diagnosis of hepatitis C virus infection in clinical laboratories? Hepatology. 1998 Jun;27(6):1700-2. | Population |
| Paydas S, Kilic B, Yavuz S, Disel U, Tanriverdi K, Sahin B, et al. Anti-HCV and HCV-RNA prevalence and clinical correlations in cases with non-Hodgkin's lymphoma. Am J Hematol. 2003;74(2):89-93. | Diagnostic test |
| Paydas S, Ergin M, Tanriverdi K, Yavuz S, Disel U, Kilic NB, et al. Detection of hepatitis C virus RNA in paraffin-embedded tissues from patients with non-Hodgkin's lymphoma. Am J Hematol. 2004 Jul;76(3):252-7. | Screening test |
| Perniola R, De RC, Leo G. Third-generation assays for hepatitis C antibodies: a four-year study of pattern changes in patients with chronic and past infection. Panminerva Med. 1999 Dec;41(4):291-4. | Population |
| Perumalswami PV, Factor SH, Kapelusznik L, Friedman SL, Pan CQ, Chang C, et al. Hepatitis outreach network: A practical strategy for hepatitis screening with linkage to care in foreign-born communities. J Hepatol. 2013;58(5):890-7. | Outcomes |
| Philip J, Sarkar RS, Kumar S, Pathak A. Changing trends of transfusion transmitted viral infections among blood donors in the last decade-a 10-year study in a large tertiary care blood bank (2000-2009). Med J Armed Forces India. 2012;68(1):28-32. | Screening test |
| Pradat P, Caillat-Vallet E, Sahajian F, Bailly F, Excler G, Sepetjan M, et al. Prevalence of hepatitis C infection among general practice patients in the Lyon area, France. European Journal of Epidemiology. 2001;17(1):47-51. | Diagnostic test |
| Quiroga JA, Avellon A, Bartolome J, Andreu M, Flores E, Gonzalez MI, et al. Detection of hepatitis C virus (HCV) core-specific antibody suggests occult HCV infection among blood donors. Transfusion. 2016 May 17. | Diagnostic test |
| Quiroga JA, Castillo I, Pardo M, Rodriguez-Inigo E, Carreno V. Combined hepatitis C virus (HCV) antigen-antibody detection assay does not improve diagnosis for seronegative individuals with occult HCV infection. J Clin Microbiol. 2006;44(12):4559-60. | Screening test |
| Rabkin CS, Tess BH, Christianson RE, Wright WE, Waters DJ, Alter HJ, et al. Prospective study of hepatitis C viral infection as a risk factor for subsequent B-cell neoplasia. Blood. 2002 Jun 1;99(11):4240-2. | Population |
| Raghuraman S, Subramaniam T, Daniel D, Sridharan G, Abraham P. Occurrence of false positives during testing for antibodies to hepatitis C virus among volunteer blood donors in India. J Clin Microbiol. 2003;41(4):1788-90. | Screening test |
| Rao HY, Ren FR, Guan WL, Houde M, Du SC, Liu CL, et al. Evaluation of the performance of the EIAgen HCV test for detection of hepatitis C virus infection. Journal of Virological | Outcomes |

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| Study | Reason for Exclusion |
|---|---|
| Methods. 2009;162(1-2):203-7. | |
| Ré V, Gallego S, Trevino E, Barbas G, Dominguez C, Elbarcha O, et al. Evaluation of five screening tests licensed in Argentina for detection of hepatitis C virus antibodies. Mem Inst Oswaldo Cruz. 2005 May;100(3):303-7. | Population |
| Reesink HW, Van der Poel CL, Cuypers HT, Lelie PN. HCV and blood transfusion. Arch Virol Suppl. 1992;4:241-3. | Population |
| Richter C, Beest GT, Gisolf EH, Van BP, Waegemaekers C, Swanink C, et al. Screening for chronic hepatitis B and C in migrants from Afghanistan, Iran, Iraq, the former Soviet Republics, and Vietnam in the Arnhem region, the Netherlands. Epidemiol Infect. 2014;142(10):2140-6. | Screening test |
| Riggert J, Schwartz DW, Uy A, Simson G, Jelinek F, Fabritz H, et al. Risk of hepatitis C virus (HCV) transmission by anti-HCV-negative blood components in Austria and Germany. Ann Hematol. 1996 Jan;72(1):35-9. | Screening test |
| Rihn B, Hussenet F, Detry MB, Catelle A, Le Faou A. Evaluation of a supplemental assay for the diagnosis of hepatitis C virus infections. Int J Infect Dis. 2000;4(1):42-5. | Population |
| Roblin DW, Smith BD, Weinbaum CM, Sabin ME. HCV screening practices and prevalence in an MCO, 2000-2007. Am J Manag Care. 2011;17(8):548-55. | Screening test |
| Rosman AS, Chinigo AS, Spungen AM, Drexler HJ, Bauman WA. Viral hepatitis in patients with spinal cord injury is explained by known risk factors. J Spinal Cord Med. 1998 Jan;21(1):25-31. | Diagnostic test |
| Ross RS, Stambouli O, Gruner N, Marcus U, Cai W, Zhang W, et al. Detection of infections with hepatitis B virus, hepatitis C virus, and human immunodeficiency virus by analyses of dried blood spots - performance characteristics of the ARCHITECT system and two commercial assays for nucleic acid amplification. Virology Journal. 2013;10(1):72. | Population |
| Roth WK, Weber M, Buhr S, Drosten C, Weichert W, Sireis W, et al. Yield of HCV and HIV-1 NAT after screening of 3.6 million blood donations in central Europe. Transfusion. 2002 Jul;42(7):862-8. | Screening test |
| Roth WK, Weber M, Seifried E. Feasibility and efficacy of routine PCR screening of blood donations for hepatitis C virus, hepatitis B virus, and HIV-1 in a blood-bank setting. Lancet. 1999;353(9150):359-63. | Outcomes |
| Saito M, Hasegawa A, Kashiwakuma T, Kohara M, Sugi M, Miki K, et al. Performance of an enzyme-linked immunosorbent assay system for antibodies to hepatitis C virus with two new antigens (c11/c7). Clin Chem. 1992 Dec;38(12):2434-9. | Population |
| Sakugawa H, Nakasone H, Nakayoshi T, Kinjo F, Saito A, Yakabi S, et al. High proportion of false positive reactions among donors with anti-HCV antibodies in a low prevalence area. J Med Virol. 1995 Aug;46(4):334-8. | Diagnostic test |
| Salmerǿn FJ, Palacios A, Perez-Ruiz M, Torres C, Oyonarte S, Fernandez-Montoya A, et al. Epidemiology, serological markers, and hepatic disease of anti-HCV ELISA-2-positive blood donors. Dig Dis Sci. 1996 Oct;41(10):1933-8. | Outcomes |
| Samimi-Rad K, Shahbaz B. Hepatitis C virus genotypes among patients with thalassemia and inherited bleeding disorders in Markazi province, Iran. Haemophilia. 2007;13(2):156-63. | Population |
| Sandesh K, Varghese T, Harikumar R, Beena P, Sasidharan VP, Bindu CS, et al. Prevalence of Hepatitis B and C in the normal population and high risk groups in north Kerala. Trop Gastroenterol. 2006 Apr;27(2):80-3. | Diagnostic test |
| Sarkodie F, Adarkwa M, du-Sarkodie Y, Candotti D, Acheampong JW, Allain JP. Screening for viral markers in volunteer and replacement blood donors in West Africa. Vox Sang. 2001 Apr;80(3):142-7. | Diagnostic test |

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| Study | Reason for Exclusion |
|---|---|
| Sato A, Ida N, Ishikawa M, Tanahashi K, Nakamura H, Sho Y, et al. A sensitive serodiagnosis of hepatitis C virus (HCV) infection with two non-fused peptides: comparison of antibody responses detected with a newly developed assay and a commercial second-generation test. Microbiol Immunol. 1993;37(4):295-304. | Population |
| Schollkopf C, Smedby KE, Hjalgrim H, Rostgaard K, Panum I, Vinner L, et al. Hepatitis C infection and risk of malignant lymphoma. Int J Cancer. 2008 Apr 15;122(8):1885-90. | Screening test |
| Schroter M, Feucht HH, Sch„fer P, Z"llner B, Polywka S, Laufs R. Definition of false-positive reactions in screening for hepatitis C virus antibodies. J Clin Microbiol. 1999 Jan;37(1):233-4. | Population |
| Schroter M, Schafer P, Zollner B, Polywka S, Laufs R, Feucht HH. Strategies for reliable diagnosis of hepatitis C infection: the need for a serological confirmatory assay. J Med Virol. 2001 Jul;64(3):320-4. | Screening test |
| Schuttler CG, Thomas C, Discher T, Friese G, Lohmeyer J, Schuster R, et al. Variable ratio of hepatitis C virus RNA to viral core antigen in patient sera. J Clin Microbiol. 2004 May;42(5):1977-81. | Population |
| Seamon MJ, Ginwalla R, Kulp H, Patel J, Pathak AS, Santora TA, et al. HIV and hepatitis in an urban penetrating trauma population: unrecognized and untreated. J Trauma. 2011 Aug;71(2):306-10. | Outcomes |
| Sears DM, Cohen DC, Ackerman K, Ma JE, Song J. Birth cohort screening for chronic hepatitis during colonoscopy appointments. Am J Gastroenterol. 2013 Jun;108(6):981-9. | Population |
| Seed CR, Kiely P, Keller AJ. Residual risk of transfusion transmitted human immunodeficiency virus, hepatitis B virus, hepatitis C virus and human T lymphotrophic virus. Intern Med J. 2005 Oct;35(10):592-8. | Screening test |
| Segbena AY, Prince-David M, Samdapawind, Kagon T, Dagnra AY. [HIV and viral hepatitis C and B in patients with sickle cell disease at the CHU Campus in Lome (Togo)]. Transfus Clin Biol. 2005;12(6):423-6. | Diagnostic test |
| Seigneres B, Descamps F, Croise R, Barlet V, Bouvier-Alias M, Chevaliez S, et al. Multicenter clinical evaluation of the new 3rd generation assay for detection of antibodies against hepatitis C virus on the VIDAS system. J Clin Virol. 2016 Mar 4;78:20-6. | Population |
| Seme K, Poljak M, Begovac J, Vince A, Tomazic J, Vidmar L, et al. Low prevalence of hepatitis C virus infection among human immunodeficiency virus type 1-infected individuals from Slovenia and Croatia. Acta Virol. 2002;46(2):91-4. | Population |
| Seremba E, Ocama P, Opio CK, Kagimu M, Thomas DL, Yuan HJ, et al. Poor performance of hepatitis C antibody tests in hospital patients in Uganda. J Med Virol. 2010 Aug;82(8):1371-8. | Screening test |
| Sethi B, Kumar S, Butola KS, Mishra JP, Kumar Y. Seroprevalence pattern among blood donors in a tertiary health care center. Internet Journal of Medical Update. 2014;9(1):10-5. | Screening test |
| Shah DO, Chang CD, Jiang LX, Cheng KY, Muerhoff AS, Gutierrez RA, et al. Combination HCV core antigen and antibody assay on a fully automated chemiluminescence analyzer. Transfusion. 2003 Aug;43(8):1067-74. | Outcomes |
| Shakeri MT, Nomani H, Mobarhan MG, Sima HR, Gerayli S, Shahbazi S, et al. The prevalence of hepatitis C virus in Mashhad, Iran: A population-based study. Hepatitis Monthly. 2013;13(3). | Screening test |
| Shang G, Seed CR, Wang F, Nie D, Farrugia A. Residual risk of transfusion-transmitted viral infections in Shenzhen, China, 2001 through 2004. Transfusion. 2007 Mar;47(3):529-39. | Screening test |
| Sharma UK, Stramer SL, Wright DJ, Glynn SA, Hermansen S, Schreiber GB, et al. Impact of changes in viral marker screening assays. Transfusion. 2003 Feb;43(2):202-14. | Diagnostic test |

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| Study | Reason for Exclusion |
|---|---|
| Sherman KE, Creager RL, O'Brien J, Sargent S, Piacentini S, Thieme T. The use of oral fluid for hepatitis C antibody screening. Am J Gastroenterol. 1994 Nov;89(11):2025-7. | Population |
| Shi H, Xie L, Shi H, Yan L, Duan Z. Characterization and application of monoclonal antibody against hepatitis C virus nonstructual protein three. Hybridoma. 2012;31(1):54-9. | Population |
| Shirachi M, Sata M, Suzuki H, Fukuizumi K, Tanikawa K, Itoh Y, et al. Evaluation of third generation anti-HCV test kit (SYNPEPT HCV-EIA II) using sera of inhabitants from HCV hyperendemic area. Kurume Med J. 1998;45(1):81-5. | Population |
| Shire AM, Sandhu DS, Kaiya JK, Oseini AM, Yang JD, Chaiteerakij R, et al. Viral hepatitis among Somali immigrants in Minnesota: Association of hepatitis C with hepatocellular carcinoma. Mayo Clin Proc. 2012;87(1):17-24. | Diagnostic test |
| Shirin H, Davidovitz Y, Avni Y, Petchenko P, Krepel Z, Bruck R, et al. Prevalence of hepatitis C virus infection in patients with lymphoproliferative disorders. Isr Med Assoc J. 2002;4(1):24-7. | Outcomes |
| Silva AE, Hosein B, Boyle RW, Fang CT, Shindo M, Waggoner JG, et al. Diagnosis of chronic hepatitis C: comparison of immunoassays and the polymerase chain reaction. Am J Gastroenterol. 1994 Apr;89(4):493-6. | Population |
| Sim¢ R, Hernandez C, Genesca J, Jard¡ R, Mesa J. High prevalence of hepatitis C virus infection in diabetic patients. Diabetes Care. 1996 Sep;19(9):998-1000. | Diagnostic test |
| Singh B, Verma M, Verma K. Markers for transfusion-associated hepatitis in North Indian blood donors: Prevalence and trends. Japanese Journal of Infectious Diseases. 2004;57(2):49-51 | Diagnostic test |
| Sinha SK, Roychoudhury S, Biswas K, Biswas P, Bandopadhyay R. Prevalence of HIV, Hepatitis B, Hepatitis C and syphilis in donor's blood: A study from eastern part of india. Open Journal of Hematology. 2012;3(1):1-6. | Diagnostic test |
| Sola R, Cruz de CE, Hombrados M, Planas R, Coll S, Jardi R, et al. Prevalence of hepatitis B and hepatitis C viruses in different counties of Catalonia, Spain: Cross-sectional study. Med Clin (Barc ). 2002;119(3):90-5. Spanish. | Language other than English or French |
| Soldan K, Davison K, Dow B. Estimates of the frequency of HBV, HCV, and HIV infectious donations entering the blood supply in the United Kingdom, 1996 to 2003. Euro surveillance : bulletin europeen sur les maladies transmissibles = European communicable disease bulletin. 2005;10(2):17-9. | Publication type |
| Sood A, Sarin SK, Midha V, Hissar S, Sood N, Bansal P, et al. Prevalence of hepatitis C virus in a selected geographical area of northern India: A population based survey. Indian J Gastroenterol. 2012;31(5):232-6. | Diagnostic test |
| Soulier A, Poiteau L, Rosa I, H,zode C, Roudot-Thoraval F, Pawlotsky JM, et al. Dried blood spots: a tool to ensure broad access to hepatitis C screening, diagnosis, and treatment monitoring. J Infect Dis. 2015 Sep 2;213(7):1087-95. | Population |
| Soverini V, Persico M, Bugianesi E, Forlani G, Salamone F, Massarone M, et al. HBV and HCV infection in type 2 diabetes mellitus: A survey in three diabetes units in different Italian areas. Acta Diabetol. 2011;48(4):337-43. | Screening test |
| Stokx J, Gillet P, De WA, Casas EC, Maendaenda R, Beulane AJ, et al. Seroprevalence of transfusion-transmissible infections and evaluation of the pre-donation screening performance at the Provincial Hospital of Tete, Mozambique. BMC Infectious Diseases. 2011;11:141. | Screening test |
| Stolz M, Gilgen M, Niederhauser C. Hepatitis C virus-polymerase chain reaction minipool testing: 3 years in the largest Swiss blood transfusion service. Vox Sang. 2003 Feb;84(2):105-10. | Screening test |
| Taliani G, Guerra E, Rosso R, Badolato MC, Luzi G, Sacco G, et al. Hepatitis C virus infection in hypogammaglobulinemic patients receiving long-term replacement therapy with | Screening test |

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| Study | Reason for Exclusion |
|---|---|
| intravenous immunoglobulin. Transfusion. 1995 Feb;35(2):103-7. | |
| Tanaka H, Hiyama T, Tsukuma H, Okubo Y, Yamano H, Kitada A, et al. Prevalence of second generation antibody to hepatitis C virus among voluntary blood donors in Osaka, Japan. Cancer Causes Control. 1994 Sep;5(5):409-13. | Screening test |
| Tashkandy MA, Khodari YA, Ibrahim AM, Dhafar KO, Gazzaz ZJ, Azab BA. Evaluation of the available anti-HCV antibody detection tests and RT-PCR assay in the diagnosis of hepatitis C virus infection. Saudi J Kidney Dis Transpl. 2007 Nov;18(4):523-31 | Population |
| Thakral B, Marwaha N, Chawla YK, Saluja K, Sharma A, Sharma RR, et al. Prevalence & significance of hepatitis C virus (HCV) seropositivity in blood donors. Indian J Med Res. 2006 Oct;124(4):431-8. | Screening test |
| Thiers V, Lunel F, Valla D, Azar N, Fretz C, Frangeul L, et al. Post-transfusional anti-HCV-negative non-A non-B hepatitis (II) serological and polymerase chain reaction analysis for hepatitis C and hepatitis B viruses. J Hepatol. 1993 Apr;18(1):34-9. | Population |
| Tillmann HL. Hepatitis C virus core antigen testing: role in diagnosis, disease monitoring and treatment. World J Gastroenterol. 2014 Jun 14;20(22):6701-6. | Publication type |
| Tobler LH, Tegtmeier G, Stramer SL, Qnan S, Dockter J, Giachetti C, et al. Lookback on donors who are repeatedly reactive on first-generation hepatitis C virus assays: Justification and rational implementation. Transfusion. 2000;40(1):15-24. | Diagnostic test |
| Tobler LH, Stramer SL, Lee SR, Masecar BL, Peterson JE, Davis EA, et al. Impact of HCV 3.0 EIA relative to HCV 2.0 EIA on blood-donor screening. Transfusion. 2003 Oct;43(10):1452-9. | Screening test |
| Tolmane I, Rozentale B, Keiss J, Arsa F, Brigis G, Zvaigzne A. The prevalence of viral hepatitis C in Latvia: a population-based study. Medicina (Kaunas). 2011;47(10):532-5. | Screening test |
| Torres MCMR, Pereira LMMB, Ximenes RAA, Araujo AS, Secaf M, Rodrigues SS, et al. Hepatitis C virus infection in a Brazilian population with sickle-cell anemia. Braz J Med Biol Res. 2003;36(3):323-9. | Population |
| Tramuto F, Mazzucco W, Maida CM, Affronti A, Affronti M, Montalto G, et al. Serological pattern of Hepatitis B, C, and HIV infections among immigrants in Sicily: epidemiological aspects and implication on public health. J Community Health. 2012 Jun;37(3):547-53. | Population |
| Trowbridge R, Sloots TP, Buda P, Faoagali J, Hyland C, Young I, et al. An ELISA for the detection of antibody to the core antigen of hepatitis C virus: use in diagnosis and analysis of indeterminate samples. J Hepatol. 1996 May;24(5):532-8. | Population |
| Tsopanomichalou M, Ergazaki M, Spandidos DA. Evaluation of western blot in routine diagnosis of hepatitis C virus. Int J Biol Markers. 1997 Jan;12(1):35-41. | Population |
| Tucker TJ, Voigt M, Bird A, Robson S, Gibbs B, Kannemeyer J, et al. Hepatitis C virus infection rate in volunteer blood donors from the Western Cape--comparison of screening tests and PCR. SAMJ, S Afr Med J. 1997 May;87(5):603-5. | Diagnostic test |
| Tulsiani S, Choudhury N, Desai P, Shah R, Mathur A, Harimoorthy V, et al. True positivity of anti-Hepatitis C Virus Enzyme-linked immunosorbent assay reactive blood donors: A prospective study done in western India. Asian J Transfus Sci. 2012 Jul;6(2):165-8. | Diagnostic test |
| van Doornum GJ, Lodder A, Buimer M, van Ameijden EJ, Bruisten S. Evaluation of hepatitis C antibody testing in saliva specimens collected by two different systems in comparison with HCV antibody and HCV RNA in serum. J Med Virol. 2001 May;64(1):13-20. | Population |
| Vardas E, Sitas F, Seidel K, Casteling A, Sim J. Prevalence of hepatitis C virus antibodies and genotypes in asymptomatic, first-time blood donors in Namibia. Bull World Health Organ. 1999;77(12):965-72. | Population |
| Varma S, Menon MC, Garg A, Malhotra P, Sharma A, Chawla YK, et al. Hepatitis C virus | Diagnostic test |

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| Study | Reason for Exclusion |
|---|---|
| infection among patients with non-Hodgkin's lymphoma in northern India. Hepatol Int. 2011 Jun;5(2):688-92. | |
| Velati C, Fomiatti L, Baruffi L, Romano L, Zanetti A. Impact of nucleic acid amplification technology (NAT) in Italy in the three years following implementation (2001-2003). Euro surveillance : bulletin europeen sur les maladies transmissibles = European communicable disease bulletin. 2005;10(2):12-4. | Screening test |
| Vermeersch P, Van RM, Lagrou K. Evaluation of the use of a combined HCV antigen/antibody assay in routine laboratory practice. Acta Clin Belg. 2010 Jul;65(4):245-7. | Population |
| Vermeersch P, Van Ranst M, Lagrou K. Validation of a strategy for HCV antibody testing with two enzyme immunoassays in a routine clinical laboratory. J Clin Virol. 2008 Aug;42(4):394-8. | Population |
| Villano SA, Vlahov D, Nelson KE, Cohn S, Thomas DL. Persistence of viremia and the importance of long-term follow-up after acute hepatitis C infection. Hepatology. 1999 Mar;29(3):908-14. | Population |
| Viner K, Kuncio D, Newbern EC, Johnson CC. The continuum of hepatitis C testing and care. Hepatology. 2015;61(3):783-9. | Screening test |
| Vivas-Arceo C, Benavides SA, De Jesus TJ, Panduro A, Rivas-Estilla AM. Hepatitis C virus: prevalence and routes of infection among blood donors of West Mexico. Hepatol Res. 2003 Feb;25(2):115-23. | Screening test |
| Vrielink H, Van der Poel CL, Reesink HW, Lelie PN. Comparison of two anti-hepatitis C virus enzyme-linked immunosorbent assays: Wellcozyme VK45 and Ortho 2.0. Infusionsther Transfusionsmed. 1995 Jun;22(3):164-7. | Screening test |
| Wang YM, Ng WC, Lo SK. Suppression of hepatitis C virus by hepatitis B virus in coinfected patients at the National University Hospital of Singapore. J Gastroenterol. 1999 Aug;34(4):481-5. | Population |
| Wang C, Zhang L, Shen X. Development of a nucleic acid lateral flow strip for detection of hepatitis C virus (HCV) core antigen. Nucleosides Nucleotides Nucleic Acids. 2013;32(2):59-68. | Population |
| Wasitthankasem R, Posuwan N, Vichaiwattana P, Theamboonlers A, Klinfueng S, Vuthitanachot V, et al. Decreasing hepatitis C virus infection in Thailand in the past decade: Evidence from the 2014 national survey. PLoS ONE. 2016;11(2). | Population |
| Watanabe J, Matsumoto C, Fujimura K, Shimada T, Yoshizawa H, Okamoto H, et al. Predictive value of screening tests for persistent hepatitis C virus infection evidenced by viraemia. Vox Sang. 1993;65(3):199-203. | Screening test |
| Watterson JM, Stallcup P, Escamilla D, Chernay P, Reyes A, Trevino SC. Evaluation of the Ortho-Clinical Diagnostics Vitros ECi Anti-HCV test: comparison with three other methods. J Clin Lab Anal. 2007;21(3):162-6. | Population |
| Widell A, Mansson AS, Sundstrom G, Hansson BG, Nordenfelt E. Hepatitis C virus RNA in blood donor sera detected by the polymerase chain reaction: comparison with supplementary hepatitis C antibody assays. J Med Virol. 1991 Dec;35(4):253-8. | Screening test |
| Widell A, Molnegren V, Pieksma F, Calmann M, Peterson J, Lee SR. Detection of hepatitis C core antigen in serum or plasma as a marker of hepatitis C viraemia in the serological window-phase. Transfus Med. 2002 Apr;12(2):107-13. | Population |
| Winkelmann M, Sorrentino JN, Klein M, Macke C, Mommsen P, Brand S, et al. Is there a benefit for health care workers in testing HIV, HCV and HBV in routine before elective arthroplasty? Orthopaedics and Traumatology: Surgery and Research. 2016;102(4):513-6. | Diagnostic test |
| Wolffram I, Petroff D, Batz O, Jedrysiak K, Kramer J, Tenckhoff H, et al. Prevalence of elevated ALT values, HBsAg, and anti-HCV in the primary care setting and evaluation of guideline defined hepatitis risk scenarios. J Hepatol. 2015 Jun;62(6):1256-64. | Population |

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| Study | Reason for Exclusion |
|---|---|
| Wu FB, Ouyan HQ, Tang XY, Zhou ZX. Double-antigen sandwich time-resolved immunofluorometric assay for the detection of anti-hepatitis C virus total antibodies with improved specificity and sensitivity. J Med Microbiol. 2008;57(8):947-53. | Population |
| Xeroulis G, Inaba K, Stewart TC, Lannigan R, Gray D, Malthaner R, et al. Human immunodeficiency virus, hepatitis B, and hepatitis C seroprevalence in a Canadian trauma population. Journal of Trauma - Injury, Infection and Critical Care. 2005;59(1):105-8. | Diagnostic test |
| Xie L, Wu XD, Huang DZ, Chen HL, He LX, Wang J, et al. Clinical application and analysis of hepatitis C virus NS3 antigen detection by ELISA in human serum. Chin Med J. 2007 Feb 20;120(4):294-9. | Population |
| Yang R, Guan W, Wang Q, Liu Y, Wei L. Performance evaluation and comparison of the newly developed Elecsys anti-HCV II assay with other widely used assays. Clin Chim Acta. 2013 Nov 15;426:95-101. | Screening test |
| Yao C, Fu Q, Xiao WH, Dong W, Yi YL. Detection of HCV infection by cPCR in patients with acute leukemia. Chin Med J. 1993 Sep;106(9):647-9. | Outcomes |
| Ye X, Yang B, Zhu W, Zheng X, Du P, Zeng J, et al. Six-year pilot study on nucleic acid testing for blood donations in China. Transfus Apher Sci. 2013;49(2):318-22. | Population |
| Yeh CT, Han CM, Lo SY, Ou JH, Fan KD, Sheen IS, et al. Early detection of anti-HCc antibody in acute hepatitis C virus (HCV) by western blot (immunoblot) using a recombinant HCV core protein fragment. J Clin Microbiol. 1994 Sep;32(9):2235-41. | Outcomes |
| Yoo SJ, Wang LL, Ning HC, Tao CM, Hirankarn N, Kuakarn S, et al. Evaluation of the Elecsys Anti-HCV II assay for routine hepatitis C virus screening of different Asian Pacific populations and detection of early infection. J Clin Virol. 2015;64:20-7. | Population |
| Yoshikawa A, Fukuda S, Itoh K, Kosaki N, Suzuki T, Hirakawa K, et al. Infection with hepatitis G virus and its strain variant, the GB agent (GBV-C), among blood donors in Japan. Transfusion. 1997 Jun;37(6):657-63. | Population |
| Younossi ZM, LaLuna LL, Santoro JJ, Mendes F, Araya V, Ravendhran N, et al. Implementation of baby boomer hepatitis C screening and linking to care in gastroenterology practices: A multi-center pilot study. BMC Gastroenterology. 2016;16(1). | Screening test |
| Zachary P, Ullmann M, Djeddi S, Meyer N, Wendling MJ, Schvoerer E, et al. Evaluation of three commercially available hepatitis C virus antibody detection assays under the conditions of a clinical virology laboratory. J Clin Virol. 2005 Nov;34(3):207-10. | Population |
| Zachary P, Ullmann M, Djeddi S, Wendling MJ, Schvoerer E, Stoll-Keller F, et al. Evaluation of two commercial enzyme immunoassays for diagnosis of hepatitis C in the conditions of a virology laboratory. Pathol Biol (Paris). 2004 Nov;52(9):511-6. | Population |
| Zani C, Pasquale L, Bressanelli M, Puoti M, Paris B, Coccaglio R, et al. The epidemiological pattern of chronic liver diseases in a community undergoing voluntary screening for hepatitis b and c. Dig Liver Dis. 2011;43(8):653-8. | Screening test |
| Zhang K, Wang L, Lin G, Li J. Is Anti-Hepatitis C Virus Antibody Level an Appropriate Marker to Preclude the Need for Supplemental Testing. Intervirology. 2015;58(5):310-7. | Population |
| Zhang HY, Kuramoto IK, Mamish D, Sazama K, Holland PV, Zeldis JB. Hepatitis C virus in blood samples from volunteer donors. J Clin Microbiol. 1993;31(3):606-9. | Population |
| Zhang HQ, Li SB, Wang GH, Chen K, Song XG, Feng XY. Detection of hepatitis C virus core antigen for early diagnosis of hepatitis C virus infection in plasma donor in China. World J Gastroenterol. 2007;13(19):2738-42. | Outcomes |
| Zotz RB, Scharf RE. Prospective analysis of blood donors for HIV-1 and HCV genomes by polymerase chain reaction. Infusionsther Transfusionsmed. 1998;25(2-3):121-5. | Screening test |
| Zuniga IA, Chen JJ, Lane DS, Allmer J, Jimenez-Lucho VE. Analysis of a hepatitis C screening programme for US veterans. Epidemiol Infect. 2006;134(2):249-57. | Screening test |

## Table 6: List of Studies Excluded From the Systematic Review — May 2016 Database Search

| Study | Reason for Exclusion |
|---|---|
| Guidelines for the screening, care and treatment of persons with hepatitis C infection. Geneva: World Health Organization; 2014 Apr. (WHO Guidelines Approved by the Guidelines Review Committee). | Publication type |

# Appendix 6: Study Characteristics

## Table 7: Study Characteristic s for the Included Study on Frequency of Harms (Q2)

| First Author (Year of Publication), Country | Funding Sources, Conflicts of Interest | Study Design | Inclusion and Exclusion Criteria | Care Setting | Study Procedure | | Outcome Measures |
|---|---|---|---|---|---|---|---|
| | | | | | Intervention | Comparator | |
| Groom (2008),[4] US | **Study:** The research service of the US Department of Veterans Affairs, Hepatitis C Resource Center Program<br><br>**Author:** Valeant Pharmaceuticals<br><br>**COI:** None declared | Retrospective database review | **Inclusion criteria:** Multiple positive tests for HCV between January 1, 1992 and December 31, 2001<br><br>**Exclusion criteria:** NR | **Screening setting:** Medical centre<br><br>**Blood test setting:** Medical centre | • Screening for risk factors for HCV<br>• Antibody testing if one or more risk factors was identified. Patients were referred for treatment | None | **Outcome(s) of interest**: Adverse events following screening and treatment<br><br>**Other outcome(s) studied:** Number of positive test results reported; incidence of unnecessary repeat testing, referral for specialty care, provision of specialty care, time between diagnosis and specialty care, virologic response; association between patient characteristics and referral rate to hepatitis clinic; reasons for non-referrals; and proportion of patients presenting at appointments for specialty HCV care and treatment. |

COI = conflict(s) of interest; HCV = hepatitis C virus; NR = not reported: Q = question.

## Table 8: Study Characteristics for the Included Study on Cost-Effectiveness (Q3)

| First Author (Year of Publication), Country | Funding Sources, Conflicts of Interest | Study Design | Inclusion and Exclusion Criteria | Care Setting | Study Procedure | | Outcome Measures |
|---|---|---|---|---|---|---|---|
| | | | | | Intervention | Comparator | |
| Wong (2015),[35] Canada | **Study:** PHAC<br><br>**COI:** One of the authors received grants and/or consulting fees from: AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck, Roche, Theravance | Cost-utility analysis | **Inclusion criteria:** Individuals living in Canada at the time of the 2011 population census<br><br>Aged 25 to 64 years old<br><br>**Exclusion criteria:** None | **Screening setting:** NR<br><br>**Blood test setting:** NR | **Primary test:** Screen + treat with pegylated interferon plus ribavirin | **Comparators**:<br>1. No screening<br>2. Screen + treat with pegylated interferon plus ribavirin-based direct-acting antiviral drugs<br>3. Screen + treat with interferon-free direct-acting antiviral drugs | **Outcome(s) of interest**:<br>ICER<br><br>**Other outcome(s) studied:** None |

COI = conflict(s) of interest; ICER = incremental cost-effectiveness ratio; NR = not reported; PHAC = Public Health Agency of Canada; Q = question.

## Table 9: Study Characteristics for the Included Studies on Patients' Preferences and Values (Q4)

| Author (Year of Publication), Country | Funding Sources, Conflicts of Interest | Study Design and Data Collection Method(s) | Inclusion and Exclusion Criteria | Study Setting | HCV Testing Setting | Recruitment Method |
|---|---|---|---|---|---|---|
| Allison et al. (2016),[58] US | NR | Descriptive survey; questionnaire | **Inclusion criteria:** Born between 1945 and 1965<br><br>**Exclusion criteria:** Unable to provide IC or use telephone interpreting services, presenting with life-threatening emergency or mental health complaint, or incarcerated | Hospital ED | Same | A list of adult ED patients was generated. Every other eligible ED patient from the list was approached, in order of length of ED stay, up to a maximum of 10 patients recruited per 4-hour block. Lists were updated every 2 hours. |
| Myers et al. (2015),[59] Canada | **Study:** Vertex Pharmaceuticals (Canada) Incorporated<br><br>**Authors:** CIHR; Alberta Innovates – Health Solutions; The Cal Wenzel Family Foundation Chair in Hepatology<br><br>**COI:** Two of the authors received grants and fees from: Vertex Pharmaceuticals (Canada) Incorporated, Hoffman-La Roche, Gilead Sciences, Janssen, | Descriptive survey; questionnaire | **Inclusion criteria:** Asymptomatic patients attending the centre for colonoscopy and colon cancer screening<br><br>**Exclusion criteria:** NR | Endoscopy unit in a non-hospital colon cancer screening centre | NR | Patients attending a colorectal cancer education session were approached to complete a voluntary, anonymous survey. |

## Table 9: Study Characteristics for the Included Studies on Patients' Preferences and Values (Q4)

| Author (Year of Publication), Country | Funding Sources, Conflicts of Interest | Study Design and Data Collection Method(s) | Inclusion and Exclusion Criteria | Study Setting | HCV Testing Setting | Recruitment Method |
|---|---|---|---|---|---|---|
| | AbbVie, Boehringer Ingelheim; other authors declared no competing interests | | | | | |
| White et al. (2015),[60] US | **Study:** NR<br><br>**Authors:** The principal investigator and research coordinator received grants from Gilead Sciences<br><br>**COI:** NR | Descriptive survey; questionnaire | **Inclusion criteria:** Medically stable, age ≥ 18 years completing ED triage, English- or Spanish-speaking, and providing IC<br><br>**Exclusion criteria:** Impaired mental status or knowledge of previous HIV or HCV infection excluded | Urban teaching hospital ED | Same | Any ED patient flagged for discharge or admission on EMR approached (low acuity discharge patient first, ending with admitted patients), eligibility confirmed and IC obtained at bedside. HCV screening protocol targeted to patients born between 1945 and 1965 and patients with a history of IDU. |
| Barocas et al. (2014),[61] US | **Study:** CTSA program through the NIH NCATS (Grant UL1TR000427); University of Wisconsin School of Medicine and Public Health Wisconsin Partnership Program<br><br>**Authors:** NIH (Grant K23DA032306); Advanced Research Fellowship through the | Multiple methods (sequential quantitative survey, then qualitative description); questionnaire and interview | **Inclusion criteria:** English-speaking adults ≥ 18 years with a history of IDU<br><br>**Exclusion criteria:** Known HCV+ infection status excluded | Multi-site SEP (office and mobile van) | Locations of testing for 329 participants tested in the past year:<br>• SEP: n = 64 (19.5%)<br>• primary care clinic: n = 107 (32.5%)<br>• correctional facility: n = 34 (10.3%) | Consecutive patients at SEP locations approached, verbal IC obtained, participants paid $10 compensation for completing survey. |

## Table 9: Study Characteristics for the Included Studies on Patients' Preferences and Values (Q4)

| Author (Year of Publication), Country | Funding Sources, Conflicts of Interest | Study Design and Data Collection Method(s) | Inclusion and Exclusion Criteria | Study Setting | HCV Testing Setting | Recruitment Method |
|---|---|---|---|---|---|---|
| | Department of Veterans Affairs<br><br>**COI:** None declared | | | | • other: n = 124 (37.7%) | |
| Hayes et al. (2014),[62] US | **Study:** NIDA Award (R01DA031056); UCSF CTSI (NIG UL1 RR024131); UCSF Liver Center (NIH P30 DK026743)<br><br>**Authors:** NIMHD (R25MD06832)<br><br>**COI:** None declared | Descriptive survey; questionnaire | **Inclusion criteria:** Age < 30-years-old, with self-reported IDU in past 30 days of baseline and self-reported negative or unknown HCV-RNA status (included HCV antibody-positive patients with unknown or negative HCV-RNA)<br><br>**Exclusion criteria:** NR | University clinical research centre | Same | NR in this study but written IC obtained; previous study of larger original cohort describes that recruitment was done by outreach workers and word of mouth. |
| Norton et al. (2014),[63] US | **Study:** The Department of Veterans Affairs AHRQ Fellowship (#T32 HS00079-01-31)<br><br>**COI:** None declared | Descriptive survey; questionnaire | **Inclusion criteria:** English-speaking, age ≥ 18 years, willing to participate in an educational intervention with a pre- and post-test survey<br><br>**Exclusion criteria:** NR | Community-based HIV/STI testing sites, homeless shelters; alcohol and drug rehabilitation centres for the homeless; and multi-service resource centre for women | NR | Convenience sample of people attending each site was surveyed. Study was advertised by leaders of each site and members chose whether to attend. Verbal IC obtained. |
| Coffin et al. (2011),[64] US | **Study:** NR<br><br>**Authors:** | Descriptive survey; questionnaire | **Inclusion criteria:** English-speaking outpatients, age ≥ 15 | 5 outpatient clinics (General Medicine, Family | 3 hypothetical screening options proposed | Sequential patients in waiting room of each outpatient clinic |

## Table 9: Study Characteristics for the Included Studies on Patients' Preferences and Values (Q4)

| Author (Year of Publication), Country | Funding Sources, Conflicts of Interest | Study Design and Data Collection Method(s) | Inclusion and Exclusion Criteria | Study Setting | HCV Testing Setting | Recruitment Method |
|---|---|---|---|---|---|---|
| | The National Institute of Allergy and Infectious Diseases training grant (5T32A1007140-33)<br><br>**COI:** None declared | | years, had not previously completed the survey<br><br>**Exclusion criteria:** NR | Medicine, Womens', General Surgery, and Orthopedics) at urban hospital and regional trauma centre | for a hospital setting: universal screening without patient knowledge of the test or receipt of results, universal screening without receipt of results but a chance to opt out of testing, or screening based on clinician judgment | approached by researchers (until 40 completed surveys from each clinic obtained), interested patients given information sheet in lieu of signed consent, completed survey in clinic room or waiting room, and given $5 compensation for survey completion. |
| Zuure et al. 2011,[65] the Netherlands | **Study:** the Netherlands Organization for Health Research and Development (ZonMw; Grant no. 6120.0016)<br><br>**COI:** None declared | Qualitative description; semi-structured interview | **Inclusion criteria:** Completed online risk assessment, identified as high-risk (e.g., blood transfusion prior to 1992, skin pierced in country with medium to high prevalence of HCV, history of IDU, living with HCV+ individual) and given advice by the online tool to get HCV testing, and provided contact information by signing up for the testing reminder service | Internet-based risk assessment tool | Participating labs affiliated with the project. Online study tool provided personalized lab requisitions. | Patients on reminder service list received an email with study invitation at 3 weeks to 3 months after initial website visit. Second email sent if no reply received within 2 weeks. Recruitment continued until data saturation reached. Verbal IC obtained before interview was started. |

## Table 9: Study Characteristics for the Included Studies on Patients' Preferences and Values (Q4)

| Author (Year of Publication), Country | Funding Sources, Conflicts of Interest | Study Design and Data Collection Method(s) | Inclusion and Exclusion Criteria | Study Setting | HCV Testing Setting | Recruitment Method |
|---|---|---|---|---|---|---|
| | | | **Exclusion criteria:** NR | | | |
| Day et al. (2008),[66] Australia | **Study:** The New South Wales health department; The National Centre in HIV Epidemiology and Clinical Research is funded by the Australian government Department of Health and Ageing<br><br>**Authors:** The National Health and Medical Research Council post-doctoral Fellowship<br><br>**COI:** NR | Descriptive survey; questionnaire | **Inclusion criteria:** Adults ≥ 18 years with a history of IDU<br><br>**Exclusion criteria:** NR | Primary care and methadone maintenance treatment centre | Same | Participants recruited directly from primary health care facility for IDU and methadone maintenance treatment centre. Posters were displayed at the centres, and ads were placed in free "street press." Process for IC not reported. |
| Khaw et al. (2007),[67] UK | **Study:** The National Treatment Agency for Substance Misuse<br><br>**COI:** None declared | Qualitative description; semi-structured interview | **Inclusion criteria:** English-speaking inmates age ≥ 18 years with a history of IDU<br><br>**Exclusion criteria:** NR | Correctional facility | Locations of previous testing for 19 participants:<br>• correctional facility: n = 11 (57.9%)<br>• hospital: n = 5 (26.3%)<br>• GP practice: n = 1 (5.3%)<br>• SEP: n = 1 (5.3%)<br>• NR: n = 1 (5.3%) | Potential participants identified from referrals to Counselling, Assessment, Referral, Advice and Throughcare Services (CARATS), or referrals to detox service, or from health assessment completed on entrance (1 method per prison). Participation was voluntary, not compensated, and participants told it would not affect treatment in |

## Table 9: Study Characteristics for the Included Studies on Patients' Preferences and Values (Q4)

| Author (Year of Publication), Country | Funding Sources, Conflicts of Interest | Study Design and Data Collection Method(s) | Inclusion and Exclusion Criteria | Study Setting | HCV Testing Setting | Recruitment Method |
|---|---|---|---|---|---|---|
| | | | | | | prison. Written IC obtained. |
| Sharp et al. (2007),[68] UK | **Study:** The Greater Glasgow Primary Care NHS Trust<br><br>**COI:** None declared | Descriptive survey; questionnaire | **Inclusion criteria:** Women attending the clinic for any reason<br><br>**Exclusion criteria:** Self-reported HCV+ status, or did not complete the survey section on "Attitudes toward Hepatitis C and testing" | 10 family planning and sexual health clinics (1 main, 9 peripheral) | Hypothetical future screening at family planning clinic proposed | Opportunistic sampling; women in the waiting area of the clinic approached by researchers to complete a questionnaire and were given an information sheet about study and HCV resources. Written IC not requested. |
| Vallabhaneni et al. (2006),[69] US | **Study:** Brown University Alpert Medical School Research Fellowship (Grant P30-AI-42854) from the NIH; Centers for AIDS Research and from the Centers for Disease Control and Prevention (Grant U50CUU11907)<br><br>**COI:** None declared | Descriptive survey; questionnaire | **Inclusion criteria:** Inmate in the correctional facility<br><br>**Exclusion criteria:** NR | Two correctional facilities (one male, one female) | Hypothetical future screening at correctional facility proposed | Participants randomly selected from the correctional facility daily roster. The first inmate selected for the day was the one whose serial number corresponded to the daily lottery number. Every subsequent 100th male inmate and every subsequent 10th female inmate on the roster was eligible for recruitment that day. IC obtained. |

AHRQ = Agency for Healthcare Research and Quality; CIHR = Canadian Institutes of Health Research; COI = conflict(s) of interest; CTSA = Clinical and Translational Science Award; CTSI = Clinical and Translational Science Institute; ED = emergency department; EMR = electronic medical record; GP = general practitioner; HCV = hepatitis C virus; IC = informed consent; IDU = injection drug use; NCATS = National Center for Advancing Translational Sciences; NIDA = National Institute on Drug Abuse; NIH = National Institutes of Health; NIMHD = National Institute on Minority Health and Health Disparities; NR = not reported; Q = question; RNA = ribonucleic acid; SEP = syringe exchange program; STI = sexually transmitted infection; UCSF = University of California, San Francisco.

## Table 10: Study Characteristics for the Included Studies on Clinical Validity of Antibody and Antigen Screening Tests (Q5)

| First Author (Year of Publication), Country | Funding Sources, Conflicts of Interest | Study Design, Enrolment Period, Care Setting, or Source of Patients | Recruitment and Patient Selection Strategy | Screening Test(s) | Diagnostic Test[a] |
|---|---|---|---|---|---|
| Lyons (2016),[70] US | Funding from pharmaceutical companies and a government grant<br><br>Authors received support and grants from multiple pharmaceutical companies, served on pharmaceutical advisory and data safety monitoring boards | Cross-sectional<br><br>January 2008 to December 2009<br><br>Urban emergency department in the Midwestern US | Cluster random sampling of patient care areas and times of day; consecutive patients within cluster approached. Compensation of $10 for blood sample and $5 for health history provided | BioChain anti-HCV ELISA (generation NR but third generation is the only version currently in production) | In-house RT-PCR, with Bio-Rad SYBR Green Ultra-Fast program; limit of detection 2.7 to 6.1 log IU/mL<br><br>All samples, irrespective of result on Ab test, were tested for RNA by RT-PCR |
| Blaxhult (2014),[71] Sweden | Study supported by the authors' institutions (hospital and university); no specific grants received<br><br>Authors declared no COI | Cross-sectional<br><br>October 2012 to March 2013<br><br>Sexually transmitted infections drop-in clinic | Sequential recruitment of unique MSM attending the clinic | ARCHITECT anti-HCV CMIA, Abbott Diagnostics | Cobas TaqMan RT-PCR, Roche |
| Sommese (2014),[72] Italy | No funding received<br><br>Authors declared no COI | Cross-sectional<br><br>January to July 2013<br><br>Division of Immunohematology, Transfusion Medicine and Transplant Immunology of the Second University of Naples | Blood donor samples selected; selection process not described. Written informed consent obtained | ARCHITECT-i2000SR immunoanalyzer), Abbott Diagnostics<br><br>Cobas e411 anti-HCV ECLIA, Roche Diagnostics<br><br>Ab tests run in parallel. Initially reactive (S/CO ≥ 1.0) or grey zone (S/CO | Cobas TaqScreen MPX RT-PCR, Roche; nominal sensitivity of < 20 IU/mL<br><br>All Ab-RR samples tested with both INNO-LIA and RT-PCR |

## Table 10: Study Characteristics for the Included Studies on Clinical Validity of Antibody and Antigen Screening Tests (Q5)

| First Author (Year of Publication), Country | Funding Sources, Conflicts of Interest | Study Design, Enrolment Period, Care Setting, or Source of Patients | Recruitment and Patient Selection Strategy | Screening Test(s) | Diagnostic Test[a] |
|---|---|---|---|---|---|
| | | | | 0.8-0.99) samples retested in duplicate for RR.<br><br>Supplementary test (for all RR samples on either or both Ab assays): INNO-LIA immunoblot, Fujirebio Diagnostics. | |
| Sommese (2014),[73] Italy | NR | Retrospective cross-sectional<br><br>2009 to 2012<br><br>Division of Immunohematology, Transfusion Medicine and Transplant Immunology of the Second University of Naples | Review of questionnaires from transfusion service and evaluation of blood samples banked during study period | ARCHITECT anti-HCV CMIA, Abbott Diagnostics<br><br>Initially reactive (S/CO ≥ 1.0) or grey zone (S/CO 0.7-0.99) samples retested in duplicate for RR.<br><br>Supplementary test (for all RR samples): INNO-LIA immunoblot, Innogenetics. | Cobas TaqScreen MPX RT-PCR on the s201 system, Roche; nominal sensitivity of < 20 IU/mL<br><br>All ARCHITECT-RR samples tested with both INNO-LIA and RT-PCR |
| Valois (2014),[74] Brazil | Funding from government grants and scholarships<br><br>Authors declared no COI | Cross-sectional<br><br>May to November 2010<br><br>Blood donation facilities (Fundação Centro de Hemoterapia e Hematologia do Pará), Belém, Brazil | Candidates for blood donation selected at private and public blood donation institutions, strategy not otherwise described | Murex anti-HCV version 4.0 ELISA (third generation), Murex Biotech Ltd. | RT-PCR with primers complementary to the conserved area of the 5' UTR of HCV |

## Table 10: Study Characteristics for the Included Studies on Clinical Validity of Antibody and Antigen Screening Tests (Q5)

| First Author (Year of Publication), Country | Funding Sources, Conflicts of Interest | Study Design, Enrolment Period, Care Setting, or Source of Patients | Recruitment and Patient Selection Strategy | Screening Test(s) | Diagnostic Test[a] |
|---|---|---|---|---|---|
| Baha (2013),[75] Morocco | Funding NR<br><br>Authors declared no COI | Cross-sectional<br><br>December 2005 to June 2011<br><br>Private and public organizations in 11 major regions in Morocco | Stratified, random cluster sampling: organizations were invited to participate by letter. Participating organizations provided member or personnel lists; every third person on potential participant lists was approached | First test: Murex anti-HCV version 4.0 ELISA (third generation), Abbott Diagnostics<br><br>Second test (performed if positive on first test): AxSYM HCV MEIA, Abbott Diagnostics<br><br>Samples considered positive if reactive on both first and second test | Cobas Ampliprep / Cobas Amplicor, Roche; limit of detection 50 IU/mL |
| Zeba (2014),[76] Burkina Faso | Funding NR<br><br>Authors declared no COI | Cross-sectional<br><br>July 2011<br><br>National Blood Transfusion Centre of Ouagadougou | Potential blood donors completed a medical history questionnaire. Eligible patients were 17- to 65-years-old, non-pregnant, weight > 50 kg, and were excluded if there was a history of previous transfusion, jaundice, or signs of hepatitis, or had engaged in high-risk sexual behaviour within past two weeks | First test: ARCHITECT Anti-HCV CMIA (on ARCHITECT-i1000SR immunoanalyzer), Abbott Diagnostics<br><br>Second test: Bio-Rad ELISA<br><br>Samples considered positive if reactive on both first and second test | RT-PCR on the GeneAmp PCR System 9700, Applied Biosystems |
| Li (2013),[77] China | Funding from university and government grants; funders were not involved | Cross-sectional<br><br>Recruitment dates NR | Proportional to population size cluster sampling among four administrative | Wantai Core Anti-HCV ELISA (third generation) | RT-PCR using the Amplicor HCV Kit, DaAn Gene Co., Ltd. |

## Table 10: Study Characteristics for the Included Studies on Clinical Validity of Antibody and Antigen Screening Tests (Q5)

| First Author (Year of Publication), Country | Funding Sources, Conflicts of Interest | Study Design, Enrolment Period, Care Setting, or Source of Patients | Recruitment and Patient Selection Strategy | Screening Test(s) | Diagnostic Test[a] |
|---|---|---|---|---|---|
| | in study design, data analysis, or manuscript preparation<br>Authors declared no COI | Urban and mostly rural Wuwei area in northwest China, with a higher than the national average incidence of HBV | divisions and classification as urban or rural (eight clusters total) | Kehua Core Anti-HCV ELISA (third generation)<br>Order of testing NR; samples considered positive if reactive on both assays | |
| Martins (2013),[78] Brazil | Study supported by government departments and agencies<br><br>Authors declared no COI | Cross-sectional<br><br>June 2010 to March 2011<br><br>Municipality of Tubarão, State of Santa Catarina, southern Brazil | Random sampling of elderly individuals enrolled in the Family Health Strategy program (which includes about 75% of elderly residents in the municipality) | VITROS Anti-HCV CLIA (on VITROS ECi), Ortho Clinical Diagnostics | Cobas Amplicor HCV Test 2.0, Roche; limit of detection 50 IU/mL |
| Woo (2013),[79] US | Testing resources provided by a clinic specializing in liver diseases, contributions for educational and promotional materials from pharmaceutical companies<br><br>COI NR | Cross-sectional<br><br>Two day event, years NR.<br><br>Asian Culture Festival, Florida | Free screening at the fair offered to voluntary attendees (parental consent required for those under 18); with a "focused approach toward those who had visible tattoos and who were from areas in which HBV and HCV are endemic, such as Thailand, Vietnam, and Laos" | VITROS Anti-HCV CLIA (on the VITROS 3600 Immunodiagnostic System), Ortho Clinical Diagnostics<br><br>Samples with S/CO > 1.0 considered positive | Cobas AmpliPrep, Roche |
| Kesli (2011),[80] Turkey | NR | Cross-sectional<br><br>October 2010 to April 2011 | Verbal and written consent obtained from patients referred to microbiology department; how they were | ARCHITECT Anti-HCV CMIA, Abbott Diagnostics<br><br>ARCHITECT HCV Ag CMIA, Abbott Diagnostics | RT-PCR assay on the Rotor-Gene 6000, QIAGEN; lower detection limit 20 IU/mL |

## Table 10: Study Characteristics for the Included Studies on Clinical Validity of Antibody and Antigen Screening Tests (Q5)

| First Author (Year of Publication), Country | Funding Sources, Conflicts of Interest | Study Design, Enrolment Period, Care Setting, or Source of Patients | Recruitment and Patient Selection Strategy | Screening Test(s) | Diagnostic Test[a] |
|---|---|---|---|---|---|
| | | Department of Microbiology, Konya Education and Research Hospital | approached or by whom NR | Both assays analyzed on the ARCHITECT-i2000SR immunoanalyzer Samples considered reactive for Ag with values ≥ 3.00 fmol/L and retested in duplicate; specimens RR (in one or both retest samples) considered Ag-positive | |
| Kesli (2009),[81] Turkey | Funding NR<br><br>Authors declared no COI | Cross-sectional<br><br>July to December 2008<br><br>Department of Microbiology, Konya Education and Research Hospital | Verbal and written consent obtained from patients referred to microbiology department; how they were approached or by whom NR | Cobas e601 anti-HCV ECLIA (third generation), Roche<br><br>ARCHITECT Anti-HCV CMIA (on the ARCHITECT i2000SR immunoanalyzer), Abbott Diagnostics | RT-PCR assay on the Rotor-Gene 6000, QIAGEN; lower detection limit 20 IU/mL |
| Rashdan (2008),[82] Jordan | NR | Cross-sectional<br><br>January 2004 to June 2006<br><br>King Abdullah University Hospital | All adult blood donors screened for HCV enrolled | Third generation anti-HCV ELISA, DiaSorin | PCR (for genotyping, not otherwise described) |
| Reis (2008),[83] Brazil | NR | Cross-sectional<br><br>March 2002 to November 2003 | NR | INNOTEST HCV Ab III ELISA, Innogenetics<br><br>Supplementary test | In-house RT-PCR with primers complementary to the conserved area of the 5' UTR of HCV |

## Table 10: Study Characteristics for the Included Studies on Clinical Validity of Antibody and Antigen Screening Tests (Q5)

| First Author (Year of Publication), Country | Funding Sources, Conflicts of Interest | Study Design, Enrolment Period, Care Setting, or Source of Patients | Recruitment and Patient Selection Strategy | Screening Test(s) | Diagnostic Test[a] |
|---|---|---|---|---|---|
| | | 12 quilombo (descendants of Afro-Brazilian slaves) remnant communities in Central Brazil; site of interview and blood sampling NR | | (performed on ELISA-positive samples): INNO-LIA HCV Ab III line immunoassay, Innogenetics | All ELISA-positive samples tested with both INNO-LIA and RT-PCR |
| Slavenburg (2008),[84] the Netherlands | Funding from Roche Nederland B.V., Woerden, the Netherlands<br><br>COI NR | Cross-sectional<br><br>June 2006<br><br>General practices in urban regions of east Netherlands | Leftover blood samples used for the study (after they had been processed for the reason blood was sent to the lab); unclear whether this was explained to patients or if consent was obtained | First test: Bioelisa HCV 4.0 ELISA (third generation), Biokit<br><br>Second test (performed if positive on first test): AxSYM HCV version 3.0 MEIA, Abbott Diagnostics<br><br>Supplementary test (performed if positive on second test): INNO-LIA HCV Score immunoblot, Innogenetics<br><br>Samples with S/CO > 1 considered positive for the assay; samples positive on both Ab tests and the supplementary immunoblot considered anti–HCV-positive | Cobas TaqMan RT-PCR, Roche; detection range 15 to 7 x $10^7$ IU/mL |
| Letowska (2004),[85] | Funding NR; assay reagents supplied by the | Cross-sectional | All blood donations collected during the study | Ortho HCV Core Antigen ELISA, Ortho Clinical | Cobas Amplicor HCV Test 2.0, Roche |

## Table 10: Study Characteristics for the Included Studies on Clinical Validity of Antibody and Antigen Screening Tests (Q5)

| First Author (Year of Publication), Country | Funding Sources, Conflicts of Interest | Study Design, Enrolment Period, Care Setting, or Source of Patients | Recruitment and Patient Selection Strategy | Screening Test(s) | Diagnostic Test[a] |
|---|---|---|---|---|---|
| Poland | manufacturer<br><br>COI NR | November 2000 to March 2001<br><br>11 regional blood centres | period were tested for HCV Ag | Diagnostics<br><br>RR samples considered positive | |
| Dalgard (2003),[86] Norway | Grants from government ministries and pharmaceutical companies<br><br>COI NR | Cross-sectional<br><br>2000 to 2001<br><br>Oslo county | Random selection from participants in the Oslo Health Study born between January and June of specific years; patients invited by letter | Ortho HCV version 3.0 ELISA, Ortho Clinical Diagnostics | In-house PCR, not otherwise described; limit of detection 500 copies/mL |
| Zervou (2003),[87] Greece | NR | Cross-sectional<br><br>January 1995 to December 1997<br><br>Blood Bank of the University Hospital of Ioannina, Epirus region of Greece | All voluntary blood donors attending the Blood Bank during study period, who passed routine pre-donation screening and were living in the Epirus region for at least 5 years before the start of the study, were recruited and informed consent obtained | Murex anti-HCV ELISA (third generation), Murex Diagnostics<br><br>Initially reactive samples retested in duplicate and RR samples considered positive for anti-HCV | RT-PCR and DEIA detect PCR products; lower detection limit of DEIA is between 10 and 100 HCV-RNA copies present in the initial sample used for reverse transcription |
| Alberti (2002),[88] Italy | Funded by the Italian National Research Council<br><br>COI NR | Cross-sectional<br><br>Recruitment dates NR<br><br>Employees of Telecom Italia | Telecom Italia proposed and promoted the study to employees and their relatives enrolled in a screening program for cardiovascular risk factors | Ortho HCV version 3.0 ELISA, Ortho Clinical Diagnostics[b]<br><br>Positive individuals retested within one month; RR persons considered anti–HCV-positive | Amplicor HCV Monitor test, Roche<br><br>Initially Ab-positive, RNA-negative samples retested for RNA at 1 and 3 months |

## Table 10: Study Characteristics for the Included Studies on Clinical Validity of Antibody and Antigen Screening Tests (Q5)

| First Author (Year of Publication), Country | Funding Sources, Conflicts of Interest | Study Design, Enrolment Period, Care Setting, or Source of Patients | Recruitment and Patient Selection Strategy | Screening Test(s) | Diagnostic Test[a] |
|---|---|---|---|---|---|
| Kondili (2002),[89] Italy | Study supported by the Ministero della Salute (Ministry of Health)<br><br>COI NR | Retrospective cross-sectional<br><br>Initial recruitment June 1983 to March 1987 for cardiovascular risk factor study; these patients were approached again at some point between 1993 and 1996 for a second serum sample for HCV testing<br><br>Four towns in central Italy | Random selection of individuals from electoral rolls; invitation to participate in study by letter | Ortho HCV version 3.0 ELISA, Ortho Clinical Diagnostics | Cobas Amplicor HCV Test 2.0, Roche; limit of detection 50 IU/mL |
| Muerhoff (2002),[90] US | NR; study conducted by research and development groups at Abbott Diagnostics | Assay performance evaluation<br><br>Dates NR<br><br>Sacramento Medical Foundation | Blood samples from volunteer blood donors obtained, not otherwise described | PRISM HCV Core Antigen CLIA, Abbott Diagnostics<br><br>RR samples considered positive<br><br>Provisional cut-off set to minimize the number of samples that tested positive, as blood donor samples were assumed to be negative for Ag | In-house RT-PCR; assay sensitivity of 800 RNA copies/mL of serum<br><br>Positive result defined as presence of a DNA fragment of the expected size in the test sample but not in any negative controls |
| Icardi (2001),[24] Italy | NR; author affiliations include Ortho Clinical Diagnostics | Assay performance evaluation<br><br>Dates and source of | Blood samples from blood donors and members of the general population obtained, not otherwise | Ortho HCV Core Antigen ELISA, Ortho Clinical Diagnostics<br>Samples considered | Cobas Amplicor HCV Test 2.0, Roche; limit of detection 50 IU/mL |

## Table 10: Study Characteristics for the Included Studies on Clinical Validity of Antibody and Antigen Screening Tests (Q5)

| First Author (Year of Publication), Country | Funding Sources, Conflicts of Interest | Study Design, Enrolment Period, Care Setting, or Source of Patients | Recruitment and Patient Selection Strategy | Screening Test(s) | Diagnostic Test[a] |
|---|---|---|---|---|---|
| | | patients NR | described | positive if RR with S/CO ≥ 1 | |
| Maio (2000),[91] Italy | Funds from the Ministero della Salute (Ministry of Health) viral hepatitis project and blood project<br><br>COI NR | Cross-sectional<br><br>June to October 1997<br><br>Buonalbergo (small town in southern Italy) | Cluster random sampling from the census (each family was a single cluster); every member of the randomly sampled families was invited to participate and informed consent obtained from all | Ortho HCV version 3.0 ELISA, Ortho Clinical Diagnostics | In-house RT-PCR with primers complementary to the conserved area of the 5' UTR of HCV; lower limit of detection was 100 genome equivalents/mL determined by the calibration with international standards |
| Lucas (1999),[92] Solomon Islands | NR | Cross-sectional<br><br>1994 to 1995<br><br>Blood bank for a tertiary referral hospital (49 bleeding stations) | Consecutive blood donors enrolled | Ortho HCV version 3.0 ELISA, Ortho Clinical Diagnostics | Amplicor PCR test, Roche |
| Guadagnino (1997),[93] Italy | Grants from the National Research Council Canada<br><br>COI NR | Cross-sectional<br><br>January to May 1996<br><br>Sersale (town in southern Italy) | Systematic 1:4 sampling procedure from the census to identify potential participants; informed consent obtained | Ortho HCV version 3.0 ELISA, Ortho Clinical Diagnostics | RT-PCR with primers complementary to the conserved area of the 5' UTR of HCV |
| Vrielink (1997),[94] the Netherlands | NR | Cross-sectional<br><br>Donations provided from May 1990 to January 1996 (ELISA version 3.0 | All adult blood donors were screened for HCV | Ortho HCV version 3.0 ELISA, Ortho Clinical Diagnostics<br>RR samples considered positive | RT-PCR, not otherwise described |

## Table 10: Study Characteristics for the Included Studies on Clinical Validity of Antibody and Antigen Screening Tests (Q5)

| First Author (Year of Publication), Country | Funding Sources, Conflicts of Interest | Study Design, Enrolment Period, Care Setting, or Source of Patients | Recruitment and Patient Selection Strategy | Screening Test(s) | Diagnostic Test[a] |
|---|---|---|---|---|---|
| | | testing only performed from April 1993 to January 1996)<br><br>Red Cross Blood Bank, Red Cross Blood Transfusion Service | | | |

Ab = antibody; Ag = antigen; CLIA = chemiluminescent immunoassay; CMIA = chemiluminescent microparticle immunoassay; COI = conflict(s) of interest; DEIA = DNA enzyme immunoassay; ECLIA = electrochemiluminescent immunoassay; EIA = enzyme immunoassay; ELISA = enzyme-linked immunosorbent assay; fmol = femtomole; HBV = hepatitis B virus; HCV = hepatitis C virus; IU = international units; L = litre; LIA = line immunoassay; mL = millilitre; MSM = men who have sex with men; NIH = National Institutes of Health; NR = not reported; PCR = polymerase chain reaction; Q = question; RNA = ribonucleic acid; RR = repeat reactivity; RT-PCR = reverse transcription polymerase chain reaction; S/CO = signal-to-cut-off ratio; UTR = untranslated region.

[a] Unless otherwise described, only samples that were considered positive on the screening test(s) received the diagnostic PCR test.

[b] Specific version of the Ortho HCV ELISA not described in the publication; however, version 3.0 was licenced at the time of publication, and other studies published around the same time used version 3.0.

# Appendix 7: Patient Characteristics

## Table 11: Patient Characteristics for the Included Study on Frequency of Harms (Q2)

| First Author (Year of Publication) | Description of Study Population | Sex n (%) | Age (Years) | Race n (%) | Marital Status n (%) | Relevant Clinical Conditions |
|---|---|---|---|---|---|---|
| Groom (2008)[4] | Patients who tested positive for HCV antibody and RNA at the Minneapolis Veterans Affairs Medical Center from January 1, 2000 to December 31, 2001 and at any other time between January 1992 and December 31, 2001.<br><br>n = 681 enrolled<br><br>n = 670 completed the study (n = 520 were viremic) | Female: 16 (3.1%) | 53.5 ± 8.4 | White: 262 (50.3%)<br>Minority (predominately African-American): 80 (15.3%)<br>Unknown: 179 (34.4%) | Married: 140 (26.9%)<br>Not married: 362 (69.6%)<br>Unknown: 18 (3.5%) | Prior psychiatric diagnosis: 179 (34.4%)<br>Prior major medical comorbidity diagnosis: 115 (22.1%)<br>Prior psychiatric prescriptions: 146 (28.0%)<br>Prior narcotic prescriptions: 117 (22.5%) |

HCV = hepatitis C virus; Q = question; RNA = ribonucleic acid.

## Table 12: Patient Characteristics for the Included Studies on Patients' Preferences and Values (Q4)

| First Author (Year of Publication) | Description of Study Population | Sex n (%) | Age in Years | Race n (%) | Education n (%) | Employment n (%) | Previous HCV Testing n (%) |
|---|---|---|---|---|---|---|---|
| Allison (2016)[58] | High prevalence birth cohort (1945 to 1965) ED patients<br><br>n = 427 | Female: 178 (42)<br>Male: 249 (58) | NR | NR | No HS diploma or less:<br>164 (38)<br>HS diploma and above:<br>262 (61) | Unemployed:<br>275 (64)<br>Employed:<br>148 (35)<br>Missing data:<br>4 (1) | NR |
| Myers (2015)[59] | High prevalence birth cohort (90.5% of study population born 1945 to 1965); 26% with ≥1 reported HCV risk factor<br><br>n = 1,012 | Male:<br>529 (52.3) | Median 56 (IQR 53 to 62) | White:<br>876 (87.1%) | University education:<br>399 (42.3%) | NR | 123 (12.2%) |
| White (2015)[60] | High prevalence birth cohort (1945 to 1965) and high-risk (history of IDU) ED patients<br><br>n = 491 | Female:<br>227 (46) | Mean 44 (SD 15) | Black:<br>248 (51%)<br>Hispanic:<br>104 (21%)<br>White:<br>76 (15%)<br>Asian:<br>32 (7%) | NR | NR | NR |
| Barocas (2014)[61] | PWID<br><br>n = 520 | Female: 163 (31)<br>Male:<br>357 (69) | Median 28 | White: 409 (83%) | Did not finish HS,<br>NT: 31 (40.3%); T: 46 (59.7%)<br>GED or HS Diploma,<br>NT: 67 (31.9%); T: 143 (68.1%)<br>Some college/ technical school, | Unemployed,<br>NT: 90 (28.3%); T: 228 (71.7%)<br>Employed, part-time,<br>NT: 23 (25.6%); T: 67 (74.4%)<br>Employed, full-time, | Patients with testing in the past year:<br>384/520 (73.8%) |

## Table 12: Patient Characteristics for the Included Studies on Patients' Preferences and Values (Q4)

| First Author (Year of Publication) | Description of Study Population | Sex n (%) | Age in Years | Race n (%) | Education n (%) | Employment n (%) | Previous HCV Testing n (%) |
|---|---|---|---|---|---|---|---|
| | | | | | NT: 29 (17.2%); T: 140 (82.4%) Graduated college/ technical school, NT: 9 (14.1%); T: 55 (85.9%) | NT: 23 (20.5%); T: 89 (79.5%) | |
| Hayes (2014)[62] | PWID<br><br>n = 129; survey respondents: n = 127 | Female: 40 (31) Male: 88 (68.2) NR: 1 (0.8) | Median 25 (IQR 23-27) | White: 74 (57.4%) Non-white: 55 (42.6%) Mixed: 27 (20.9%) Latino/Hispanic: 7 (5.4%) African-American: 5 (3.9%) Native American: 5 (3.9%) Asian and Filipino: 2 (1.6%) Other: 9 (7%) | Completed Grade 12: Yes: 93 (72%) No: 36 (28%) | NR | NR |
| Norton (2014)[63] | High-risk urban population (poor, marginalized, many current/former PWID)<br><br>n = 140 | Female: 48 (34) Male: 92 (66) | Median 46 (IQR 33 to 54) | White: 37% Black: 57% Other: 6% | Elementary: 16% HS: 39% Some college: 31% Finished college: 14% | NR | NR |
| Coffin (2011)[64] | General population | Female: 55% | Median 47 (range 18-82) | White: 112 (56%) | NR | NR | 102 (51%) |

## Table 12: Patient Characteristics for the Included Studies on Patients' Preferences and Values (Q4)

| First Author (Year of Publication) | Description of Study Population | Sex n (%) | Age in Years | Race n (%) | Education n (%) | Employment n (%) | Previous HCV Testing n (%) |
|---|---|---|---|---|---|---|---|
| | (various outpatients); subset with risk factors:<br>History of IDU: 23 (12%)<br>History of blood transfusion: 39 (20%)<br><br>n = 200 | Male: 45% | | African-American or African:<br>65 (33%)<br>Hispanic or Latino:<br>16 (8%) | | | |
| Zuure (2011)[65] | High-risk members recruited from a general population<br><br>n = 33 | Female:<br>26 (79) | Median 49 (IQR 41 to 62) | NR | Low: 22%<br>Moderate:19%<br>High: 59% | NR | NR |
| Day (2008)[66] | PWID<br><br>n = 229; recently tested for HCV:<br>n = 166 | Female:<br>70 (30.5)<br>Male:<br>151 (65.9)<br>Trans-gender:<br>8 (3.5) | Median 36 (range 19-58) | White:<br>177 (77.3%)<br>Aboriginal/ Torres Strait Islander:<br>31 (13.5%)<br>Asian:<br>3 (1.3%)<br>Other:<br>18 (7.9%) | Completed Year 10:<br>Yes: 168 (73.3%)<br>No: 60 (26.2%) | Employed/ other:<br>46 (20%)<br>Unemployed: 177 (77%) | 166 (72%) |
| Khaw (2007)[67] | Inmates<br><br>n = 30 | Female:<br>5 (17)<br>Male: 25 (83) | NR | NR | NR | NR | 19 (63%) |

## Table 12: Patient Characteristics for the Included Studies on Patients' Preferences and Values (Q4)

| First Author (Year of Publication) | Description of Study Population | Sex n (%) | Age in Years | Race n (%) | Education n (%) | Employment n (%) | Previous HCV Testing n (%) |
|---|---|---|---|---|---|---|---|
| Sharp (2007)[68] | General population (women attending FPC)<br><br>n = 964 | Female: 964 (100) | Range 14-55 | White: 929 (97%)<br>Other: 29 (3%) | School: 463 (48%)<br>College: 167 (17%)<br>University: 245 (25%)<br>No qualification: 53 (6%) | In education: 231 (24%)<br>In employment: 631 (66%)<br>Unemployed: 97 (10%) | NR; 2 patients excluded from analysis because they reported being HCV-positive |
| Vallabhaneni (2006)[69] | Inmates; History of IDU 44 (29%) History of sharing needles: 28 (19%)<br><br>n = 153 | Female: 53 (35)<br>Male: 100 (65) | Mean 30.4 (± 8.9) | White: 64 (42%)<br>Black: 40 (26%)<br>Hispanic: 32 (21%)<br>Other: 17 (11%) | Less than HS: 57 (37%)<br>HS or equivalent: 60 (39%)<br>Some college: 36 (24%) | NR | 41 (26.8%) |

DTA = diagnostic test accuracy; ED = emergency department; FPC = family planning clinic; GED = general educational development; HCV = hepatitis C virus; HS = high school; IDU = injection drug use; IQR = interquartile range; NR = not reported; NT = not tested in past 12 months; PWID = people who inject drugs; Q = question; SD = standard deviation; T = tested in past 12 months.

## Table 13: Patient Characteristics for the Included Studies on Clinical Validity of Screening with Antibody and Antigen Tests (Q5)

| First Author (Year of Publication), Country | Description of Study Population | Eligible Patients, N | Included Patients, n | Female, n (%) | Male, n (%) | Age (Years) | Race, n (%) | Risk Factors or Relevant Clinical Condition, n (%) |
|---|---|---|---|---|---|---|---|---|
| Lyons (2016),[70] US | Adult patients attending an urban emergency department | 1,934 | 924 | 457 (49.5) | 467 (50.5) | 18 to 29: n = 265<br>30 to 39: n = 172<br>40 to 49: n = 217<br>20 to 64: n = 261<br>NR: n = 8 | Black: 503 (54.4)<br>White: 380 (41.1)<br>Hispanic: 28 (3.0)<br>Other/NR: 41 (4.4) | Lifetime history of IDU: 69 (7.5)<br>HIV+: 27 (2.9)<br>Lifetime history of hepatitis: 69 (7.5)<br>Known HCV infection: 48 (5.2) |
| Blaxhult (2014),[71] Sweden | MSM attending a drop-in STI clinic, without known HIV or HCV infection | 1,061 | 1,008 | 0 | 1,008 (100) | Median: 33<br>Range: 16 to 82 | NR | NR |
| Sommese (2014),[72] Italy | Volunteer blood donors | NR | 840 | 275 (32.7) | 564 (67.3) | Mean: 37.8 (SD 12.5) | NR | NR |
| Sommese (2014),[73] Italy | Apparently healthy, first-time, and repeat adult volunteer blood donors | NR | 17,912 | NR | NR | Mean: 42.5 (SD 24.7)<br>Range: 25 to 60 | NR | NR |
| Valois (2014),[74] Brazil | Adult candidates for blood donation (HCV-infected and uninfected) | 13,772 | 13,772 | 3,045 (22.1) | 10,727 (77.9) | 18 to 22: n = 2,871 23 to 29: n = 3,427 30 to 39: n = 4,149 40 to 49: n = 2,907 50 to 60: n = 418 | NR | Study identified variables associated with HCV infection using univariate analysis |
| Baha (2013),[75] Morocco | Apparently healthy individuals from the general population | 41,311 | 41,269 | 12,506 (30.3) | 28,763 (69.7) | Mean: 45 (SD 10.9)<br>Range: 5 to 84 | NR | Study identified variables associated with HCV infection using univariate analysis |

## Table 13: Patient Characteristics for the Included Studies on Clinical Validity of Screening with Antibody and Antigen Tests (Q5)

| First Author (Year of Publication), Country | Description of Study Population | Eligible Patients, N | Included Patients, n | Female, n (%) | Male, n (%) | Age (Years) | Race, n (%) | Risk Factors or Relevant Clinical Condition, n (%) |
|---|---|---|---|---|---|---|---|---|
| Zeba (2014),[76] Burkina Faso | Asymptomatic, non-pregnant, volunteer blood donors aged 17 to 65 | NR | 2,200 | NR | NR | NR | NR | HIV+: 1 (0.05) |
| Li (2013),[77] China | Members of the general population (85% from rural areas) | NR | 7,189 | 4,084 (56.8) | 3,105 (43.2) | Mean : 37.6 (SD 10)<br>Range: 1 to 77<br>(≤ 20: 28.8%) | NR | Study identified variables associated with HCV infection using univariate analysis |
| Martins (2013),[78] Brazil | Elderly (age 60 and older) individuals from the general population | 1,015 | 820[a] | 504 (61.5) | 316 (38.5) | Mean: 68.6 (SD 7.0) | White: 756 (92.4) | History of drug use: 3 (0.4)<br>Transfusion before 1993: 64 (7.8) |
| Woo (2013),[79] US | Attendees at a cultural fair | 9,000 | 231 | 137 (59) | 93 (40) | < 18: n = 12<br>18 to 44: n = 84<br>45 to 65: n = 99<br>> 65: n = 21<br>NR: n = 15 | Hispanic: 90 (39)<br>Non-Hispanic White: 72 (31)<br>Asian: 51 (22)<br>Black: 13 (6)<br>NR: 7 (3) | History of hepatitis: 10 (4)<br>Family history of hepatitis: 20 (9) |
| Kesli (2011),[80] Turkey | Patients at low risk for HCV infection referred to a hospital microbiology department | NR | 212 | 122 (57.5) | 90 (42.5) | Mean: 59 (SD 14.5) | NR | NR |
| Kesli (2009),[81] Turkey | Patients at low risk for HCV infection referred to a hospital | NR | 7,156 | 3,814 (53.3) | 3,342 (46.7) | Mean: 45.2 (SD 18.4)<br>(0 to 29: 0.04%) | NR | NR |

## Table 13: Patient Characteristics for the Included Studies on Clinical Validity of Screening with Antibody and Antigen Tests (Q5)

| First Author (Year of Publication), Country | Description of Study Population | Eligible Patients, N | Included Patients, n | Female, n (%) | Male, n (%) | Age (Years) | Race, n (%) | Risk Factors or Relevant Clinical Condition, n (%) |
|---|---|---|---|---|---|---|---|---|
| | microbiology department | | | | | | | |
| Rashdan (2008),[82] Jordan | All first-time adult blood donors without chronic medical problems and with low pretest probability of HCV infection | 14,236 | 14,236 | 570 (4.0) | 13,666 (96.0) | NR | NR | NR |
| Reis (2008),[83] Brazil | Members of the general population in quilombo (descendants of Afro-Brazilian slaves) remnant communities | NR | 1,007 | 527 (52.3) | 480 (47.7) | Mean: 29.9<br>Median: 24 | NR | IDU: 0<br>Imprisonment: 18 (1.8)<br>Familial hepatitis: 265 (26.4) |
| Slavenburg (2008),[84] the Netherlands | Persons visiting general practices who had been referred to a servicing laboratory by the physician for blood analysis of biochemical parameters[b] | NR | 2,200[c] | 1,254 (57) | 928 (42.2) | Mean: 60.4 (SD 16.6) | NR | NR |
| Letowska (2004),[85] Poland | Blood donors | 133,279 | 133,279 | NR | NR | NR | NR | NR |
| Dalgard (2003),[86] Norway | Members of the general population born between January and June of 1924, 1925, 1940, 1941, 1955, 1960, and 1970 | 24,448 | 11,456 | 6,509 (56.8) | 4,947 (43.2) | 30: n = 2,456<br>40: n = 2,161<br>45: n = 1978<br>59/60: n = 2,881<br>75/76: n = 1,980 | NR | Known HCV infection: 32 (0.3)<br>Previous treatment for HCV: 9 (0.1) |

## Table 13: Patient Characteristics for the Included Studies on Clinical Validity of Screening with Antibody and Antigen Tests (Q5)

| First Author (Year of Publication), Country | Description of Study Population | Eligible Patients, N | Included Patients, n | Female, n (%) | Male, n (%) | Age (Years) | Race, n (%) | Risk Factors or Relevant Clinical Condition, n (%) |
|---|---|---|---|---|---|---|---|---|
| Zervou (2003),[87] Greece | Healthy adult one-time and repeat blood donors at low risk for HCV living (passed pre-donation screening; no history of IDU). Only the first blood donation from each patient obtained during the study period was included | 6,696 | 6,696 | 1,401 (21) | 5,295 (79) | Median: 36<br>Range: 18 to 60 | NR | NR |
| Alberti (2002),[88] Italy | Asymptomatic adults (employees of Telecom Italia and their relatives) | NR | 4,820 | 2,688 (55.8) | 2,132 (44.2) | Range: 16 to 60 | NR | NR |
| Kondili (2002),[89] Italy | Adults from the general population enrolled in a study on cardiovascular risk factors | 11,299[d] | 2,032 | NR | NR | Range: 20 to 69[d] | NR | NR |
| Muerhoff (2002),[90] US | Volunteer blood donors who had not been screened for HCV antibodies | NR | 1,004 | NR | NR | NR | NR | NR |
| Icardi (2001),[24] Italy | Sera samples from: (a) blood donors, and (b) the general population | NR | (a) 2,586<br>(b) 500 | NR | NR | NR | NR | NR |
| Maio (2000),[91] Italy | Members of the general population older than 5 years | 532 | 488 | 252 (51.6) | 236 (48.4) | Mean: 42.9<br>Range: 6 to 87<br>(6 to 29: 16.6%) | NR | Study identified variables associated with HCV infection using univariate |

## Table 13: Patient Characteristics for the Included Studies on Clinical Validity of Screening with Antibody and Antigen Tests (Q5)

| First Author (Year of Publication), Country | Description of Study Population | Eligible Patients, N | Included Patients, n | Female, n (%) | Male, n (%) | Age (Years) | Race, n (%) | Risk Factors or Relevant Clinical Condition, n (%) |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | analysis |
| Lucas (1999),[92] Solomon Islands | Blood donors | 598 | 598 | 102 (17.1) | 496 (82.9) | Range: 16 to 59<br>Mean (HCV+): 24.6 (SD 11.1)<br>Mean (HCV–): 25.9 (SD 10.0) | NR | Previous jaundice: 30 (5) |
| Guadagnino (1997),[93] Italy | Members of the general population | 1,400 | 1,352 | 771 (57) | 581 (43) | 0 to 9: n = 106<br>10 to 19: n = 162<br>20 to 29: n = 184<br>30 to 39: n = 215<br>40 to 49: n = 161<br>50 to 59: n = 152<br>≥ 60: n = 372 | NR | Study identified variables associated with HCV infection using multiple logistic regression analysis |
| Vrielink (1997),[94] the Netherlands | First-time and repeat volunteer blood donors | 529,483 (total)<br>262,090 (ELISA version 3.0) | 529,483 (total)<br>262,090 (ELISA version 3.0) | NR | NR | NR | NR | NR |

ELISA = enzyme-linked immunisorbent assay; HCV = hepatitis C virus; IDU = injection drug use; MSM = men who have sex with men; NR = not reported; Q = question; SD = standard deviation; STI = sexually transmitted infection.

[a] Excludes 73 individuals who completed a structured questionnaire-based interview regarding sociodemographic characteristics, medical history, and risk behaviours, but who did not attend blood screening.

[b] Clinical status of the patients NR; however, leftover blood from these requisitioned blood tests was used for the study, suggesting that these patients were not suspected to have HCV and that this was not the primary purpose of blood testing.

[c] Demographic data unavailable for 18 patients; all tested negative for HCV with the study test strategy.

[d] At recruitment for the original study on cardiovascular risk factors. A total of 3,884 patients agreed to participate in the original study between 1983 and 1987.

# Appendix 8: Risk of Bias Assessments

## Table 14: Summary Critical Appraisal of Cost-Effectiveness Study (Q3)

| Domain | Strengths | Limitations |
|---|---|---|
| Wong et al. (2015)[35] | | |
| **Study Design** | • The viewpoint of the analysis was that of a payer, and it was justified based on projected increase in uptake of better and costlier treatment options.<br>• A country-specific study was justified because of differences in epidemiology and health care systems between Canada and countries in which cost-effectiveness analyses had been completed.<br>• The rationale for choosing alternative programs or interventions compared was based on Canadian guidelines and results of phase III clinical trials.<br>• The alternatives being compared were clearly described.<br>• The form of economic evaluation used was stated. | • A research question specific to this study was not stated. The objective of the study was to develop a model for projecting health and economic outcomes of various treatment strategies.<br>• It is unclear whether the economic importance of the research question was stated. |
| **Data Collection** | • The sources of effectiveness estimates used were stated.<br>• Details of the design and results of the effectiveness study were given.<br>• Details of the methods of synthesis of estimates were given.<br>• The primary outcomes measures for the economic evaluation were clearly stated.<br>• Methods to value benefits were stated.<br>• Quantities of resources used were reported separately from their unit costs.<br>• Methods for the estimation of quantities and unit costs were described.<br>• Currency and price data were recorded.<br>• Citations were provided for details of models used. | • Details of the subjects from whom valuations were obtained were not given within the study.<br>• Details of currency of price adjustments for inflation or currency conversion were not given.<br>• The choice of the economic evaluation and the model used were not justified.<br>• Although the sources of the key model parameters were described in detail and cited, the selection of each parameter was not justified.<br>• The study was not explicit in reporting which parameters were Canadian-specific and which were based on other populations. |
| **Analysis and Interpretation of Results** | • The discount rate was stated.<br>• The approach to sensitivity analysis was given.<br>• The choice of variables for the sensitivity analysis were justified.<br>• The ranges over which the variables are varied were justified.<br>• Relevant alternatives were compared.<br>• The incremental analysis was reported.<br>• Major outcomes were presented in a disaggregated as well as an aggregated form.<br>• Conclusions were accompanied by the appropriate caveats. | • The time horizon of costs and benefits was not stated. |

Q = question.

## Table 15: Summary Critical Appraisal of Studies on Patients' Preferences and Values (Q4)

| Author, Publication Year | Major Strengths | Major Limitations |
|---|---|---|
| **Surveys** | | |
| Allison et al. (2016)[58] | • A sample size calculation was provided.<br>• The questionnaire is adapted from a previous study and was pilot-tested in patients. | • The target population is baby boomers attending an emergency department at one hospital, and the majority of study participants were not working or born outside of the US; this is unlikely to be representative of the larger population of baby boomers, or even of baby boomers attending hospitals for other reasons.<br>• The sampling strategy used was likely to introduce selection bias; every second patient within a block of patients identified within a time frame was approached to participate in the study. No description was provided to describe who was recruiting participants, and it is possible some channelling bias was occurring.<br>• Insufficient detail was provided regarding the qualitative analysis, and it is unclear if all reasons for not testing (the only open-ended question) were reported.<br>• Study authors did not draw appropriate linkages between the data and the conclusions. The conclusions were broad and reaching, and perhaps not congruent with the data that they presented. |
| Myers et al. (2015)[59] | • A large sample was gathered to explore the issue of feasibility of birth cohort screening.<br>• The study was conducted in a Canadian setting. | • The target population is visitors to an endoscopy unit in a non-hospital setting, which is not representative of the population eligible for birth cohort screening. People who do not adhere to colorectal cancer screening guidelines are not included.<br>• No attempt was made to explore the perspectives of people who did not consent to testing. These perspectives seem critical to the question of feasibility of birth cohort screening. In this study, 10% of people refused to have their serum tested for HCV.<br>• No description was provided regarding the validity or reliability of the questionnaire. There is a concern regarding their validity in relation to the research question since issues such as preferences or reasons for or against testing are not addressed. Topics address some sensitive information (e.g., risk behaviours), as well as some that could be prone to recall bias (e.g., previous testing and previous diagnoses). Reliability in responses is therefore questionable. |
| White et al. (2015)[60] | • A large sample was obtained.<br>• The research question is novel and suitable to be addressed through a survey design.<br>• A pilot test was conducted. | • Generalizability is unlikely given this survey was conducted at a large, urban, academic centre, and therefore the translation of results to other emergency departments is questionable.<br>• Validity and reliability are not discussed, although the |

## Table 15: Summary Critical Appraisal of Studies on Patients' Preferences and Values (Q4)

| Author, Publication Year | Major Strengths | Major Limitations |
|---|---|---|
| | • Research assistants who administered the survey were trained and blinded to any test results and reason for patients' visits. | survey was adapted from one previously used at the CDC.<br>• Social desirability bias is a potential, with participants perhaps likely to indicate they are willing to be screened if approached by research staff. |
| Hayes et al. (2014)[62] | • Interviewers were trained with experience in HIV and HCV testing protocols and risk reduction counselling, increasing the likelihood for rapport between researchers and participants and therefore potentially increasing participation and decreasing social desirability bias.<br>• Recruitment was conducted by outreach workers and by word of mouth, which could increase the likelihood for participation by those who are not as likely to access health care services. | • Only those who were already seeking and engaged in screening were included; the results do not represent people who were not willing to be screened.<br>• The recruitment rate was not reported, raising the potential for systematic differences in perspectives between those who did and did not participate. Two reported reasons for non-participation include refusal and not returning for test results, suggesting that testing preferences could be different between those who did and did not participate.<br>• For questions related to testing preferences, fixed-choice responses were used, although these questions are better suited to an open-ended format to allow participants to express their views as opposed to responding to researcher-developed questions. |
| Norton et al. (2014)[63] | • The study was thoughtfully designed, including calculation of an appropriate sample size, and conducting a pilot test before survey administration.<br>• Study reporting was comprehensive and included a thorough discussion of limitations and potential biases. | • The study was exempted from requiring ethics review and approval, yet the study population represented a marginalized and vulnerable group (PWID, homeless people).<br>• A convenience sample was obtained, and a financial incentive was provided, raising concerns for selection bias.<br>• Although acknowledged as a limitation, the results are likely not generalizable, as a convenience sample would not likely have included people with a variety of attitudes toward screening and specifically those who are not motivated to participate.<br>• The inclusion criteria included high-risk individuals who were already accessing treatment and rehabilitation services, and therefore generalizability is a concern because of the exclusion of those who do not access health care services.<br>• Social desirability bias is a potential because of the researcher-participant relationship and since the questionnaire was administered in person. The acceptability of HCV screening would have been overestimated in this case, especially in the scenario where participants were asked about screening even if they couldn't get treatment. |
| Coffin et al. (2011)[64] | • This survey included participants from five clinics representative of outpatient care, and received a high response rate.<br>• A pilot test was conducted, and the | • It is unclear if the sample is representative of the US general population, and would exclude those who do not access health care services, including the healthy and the marginalized.<br>• Given the nature of the questions, there is potential for |

## Table 15: Summary Critical Appraisal of Studies on Patients' Preferences and Values (Q4)

| Author, Publication Year | Major Strengths | Major Limitations |
|---|---|---|
| | questions asked appear to have face validity. | inconsistency in responses over time and between hospital records (e.g., test status).<br>• As the study sample represented people already accessing health care, and the questionnaire did not explore reasons for refusing screening, the results do not adequately support the conclusions that "patients support universal testing for HCV" and "that patients appear to place a higher priority on being tested than they do on the process of informed consent or the receipt of negative results." |
| Day et al. (2008)[66] | • This survey used a combination of open-ended and closed-ended questions to elicit participants' preferences regarding screening, and their experiences with the process.<br>• A large sample was obtained that includes both PWID who regularly access health care services at a primary health care centre, as well as people who might not and who were recruited through the "street press". | • The sample included only people who consented to testing and therefore those who did not consent are not represented, although this group would likely hold different perspectives than those who agreed to testing.<br>• Social desirability bias is a potential concern, given the sensitive nature of the topic.<br>• No indication is provided in regards to a response rate or reasons for non-participation. |
| Sharp et al. (2007)[68] | • The investigators compiled a large sample with a high (approximately 96%) participation rate. | • There is unclear validity of survey questions, and it is unclear whether an exhaustive list of factors was assessed or whether participants had the opportunity to identify factors not on the list.<br>• One objective relates to determining whether family planning clinics are an acceptable screening location; however, only the opinion of people accessing these clinics were included.<br>• Selection bias is a potential since the Research Assistant was present for only 15 hours of the week to recruit participants, and it is possible that people with differing opinions on HCV screening could be missed if they systematically attended the clinic outside these hours.<br>• It is unclear how the survey was administered; for example, when women were approached (before or after appointments?), when they were given the information sheet (before or after the questionnaire?) and whether the questionnaire was completed with the support of an administrator, all of which could impact the reliability of responses.<br>• There is unclear generalizability to women attending family planning clinics in Glasgow, and whether a variety of clinics that would be accessed by a range of women were included.<br>• Conclusions were reached by extrapolating results to |

## Table 15: Summary Critical Appraisal of Studies on Patients' Preferences and Values (Q4)

| Author, Publication Year | Major Strengths | Major Limitations |
|---|---|---|
| | | infer concern by women over passing on HCV to their children, although this question was not directly asked of participants. |
| Vallabhaneni et al. (2006)[69] | • A prisoner served as a representative on the ethics review board, increasing confidence that the study methods were appropriate from the perspective of participants.<br>• A high participation rate was obtained. | • A survey design was appropriate, although it didn't allow the inmates to express their attitudes in their own words.<br>• This was an interviewer-administered questionnaire and the reliability of results would have been impacted by the rapport between the inmate and the interviewer, and could vary by interviewer. Social desirability bias is a concern, in particular relation to questions about injection drug use, HCV testing, and HCV treatment.<br>• Validity and reliability in the survey questions was not discussed, and a pilot test was not conducted to refine study methods. |
| **Qualitative Description** | | |
| Zuure et al. (2011)[65] | • A qualitative approach is appropriate to understand from the perspective of people accessing this service, their motivations for wanting to understand their HCV risk, and for compliance and non-compliance with screening recommendations.<br>• Semi-structured, telephone interviews were an appropriate and rigorous method to gather data.<br>• Ethical issues considered including consent, withdrawal, confidentiality, and approval by an ethics review board.<br>• A rigorous analysis plan was outlined, including iterative data collection and analysis, sampling until data saturation, and provision of verbatim quotes to support results. | • Novel intervention (an Internet-mediated blood screening service), with limited applicability to other settings.<br>• It is unclear how the online project from which the participants were recruited was promoted and therefore what subset of the population might be represented in this sample, and whose views might be missing.<br>• No description was provided regarding the researchers' background and the impact this might have on the research approach and the analysis. |
| Khaw et al. (2007)[67] | • The study results may be used to bring an HCV screening program to a vulnerable population.<br>• The use of interviews allowed for the perspectives of prisoners to be collected as data, as opposed to researcher-driven issues. | • There are no criteria reported by which participants were selected into the study, raising the concern that people were not purposively selected as is typical in qualitative research and as is reported by the authors.<br>• Little information was provided regarding the interview process, including whether the interviews were structured, semi-structured or unstructured, what the questions were, and what training, if any, the interviewer had in terms of interviewing and also with this population.<br>• No description was provided regarding the researcher's role or relationship with the prison system, |

## Table 15: Summary Critical Appraisal of Studies on Patients' Preferences and Values (Q4)

| Author, Publication Year | Major Strengths | Major Limitations |
|---|---|---|
| | | how access was gained to the research sites, and how any of this could influence the data that were collected, or the analysis. It can be assumed that the researchers feel that HCV testing in prisons is a good goal and it is unclear whether the researchers did, or were able to, bracket this assumption during the interviews and analysis.<br>• Only a brief description is provided regarding the analysis strategy, and it is therefore unclear if all three researchers analyzed all transcripts, or whether some or all were double-coded. It is also unclear what constituted a "theme," and what sorts of discussions, if any, took place among the research team to confer authenticity on emerging themes. No mention is made of efforts to enhance the credibility of results. Several supportive quotes are provided, but the accompanying textual description is very much in the language of the researchers as opposed to the participants.<br>• In general, appropriate ethical practices were followed for this unique population, although the use of first names in the presentation of results introduces a risk for the maintenance of confidentiality. |
| **Mixed-Methods (Survey and Qualitative Description)** | | |
| Barocas et al. (2014)[61] | • A large sample was obtained, including vulnerable participants.<br>• The study will help to address an important issue in the community.<br>• The analysis is well-done. | • The questionnaire used in this study was not validated, nor was appropriateness of the language or content in this population discussed.<br>• PWID were recruited from a free-needle exchange program, which is likely to be accessed by a group of PWID who are more likely to access health services in general and therefore miss those who are hesitant to access such care and perhaps have different perceptions in terms of perceived barriers and facilitators.<br>• The researchers do not report any attempt to position themselves within the study, nor describe how their position might have impacted on the study conduct, in particular regarding data collected through interviews.<br>• Another concern regards the process of informed consent, and the potential for coercion with the cash incentive for participation, which were not discussed.<br>• No attempt was made to integrate the qualitative results with the quantitative results. This is a missed opportunity to explore how the characteristics that emerged as related to screening behaviour through the survey data related to participant accounts through the interviews. The interview data could help explain the significance of those characteristics and why they may or may not translate into increased screening. |

CDC = Centers for Disease Control and Prevention; HCV = hepatitis C virus; PWID = people who inject drugs.

## Table 16: Summary Critical Appraisal of Studies on Clinical Validity of Screening Tests (Q5)

| First Author (Year) | Risk of Bias | | | | Applicability Concerns | | |
|---|---|---|---|---|---|---|---|
| | Patient Selection | Screening Test (Ab or Ag) | Diagnostic Test (PCR) | Flow and Timing | Patient Selection | Screening Test (Ab or Ag) | Diagnostic Test (PCR) |
| Lyons (2016)[70] | Low | Unclear | Low | Low | Low[a] | Low | Low |
| Blaxhult (2014)[71] | Low | Unclear | Unclear | Low | Low[b] | Low | Low |
| Sommese (2014)[72] | Unclear | Low | Low | Low | Low | Low | Low |
| Sommese (2014)[73] | Unclear | Low | Low | Low | Low | Low | Low |
| Valois (2014)[74] | Low | Unclear | Unclear | Low | Low | Low | Low |
| Baha (2013)[75] | Low | Unclear | Low | Unclear | Low | Low | Low |
| Zeba (2014)[76] | Low | Unclear | Low | Low | Low | Low | Low |
| Li (2013)[77] | Low | Unclear | Low | Low | Low[a] | Low | Low |
| Martins (2013)[78] | Low | Unclear | Low | Low | Low[a,c] | Low | Low |
| Woo (2013)[79] | High[d] | Low | Unclear | Low | Low[d] | Low | Low |
| Kesli (2011)[80] | Unclear[e] | Low | Low | Low | Unclear[e] | Low | Low |
| Kesli (2009)[81] | Unclear | Low | Low | Low | Low | Low | Low |
| Rashdan (2008)[82] | Low | Low | Unclear | Low | Low | Low | Low |
| Reis (2008)[83] | Unclear | Unclear | Low | Low | Unclear[a,f] | Low | Low |
| Slavenburg (2008)[84] | Unclear | Unclear | Low | Low | Unclear[g] | Low | Low |
| Letowska (2004)[85] | Low | Low | Unclear | Low | Low | Low | Low |
| Dalgard (2003)[86] | Low | Unclear | Low | Low | Low[a] | Low | Low |
| Zervou (2003)[87] | Low | Unclear | Low | Low | Low | Low | Low |
| Alberti (2002)[88] | Low | Unclear | Unclear | Low | Low | Low | Low |
| Kondili (2002)[89] | High[g] | Low | Low | Low | High[h] | Low | Low |
| Muerhoff (2002)[90] | Low | High[h] | Low | Low | Low | Unclear[i] | Low |
| Icardi (2001)[24] | Unclear | Low | Low | Low | Low | Low | Low |
| Maio (2000)[91] | Low | Low | Low | Low | Low[a] | Low | Low |
| Lucas (1999)[92] | Low | Unclear | Unclear | Low | High[j] | Low | Low |
| Guadagnino (1997)[93] | Low | Low | Unclear | Low | Low[a] | Low | Low |
| Vrielink (1997)[94] | Low | Unclear | Unclear | Unclear | Low | Low | Low |

Ab = antibody; Ag = antigen; PCR = polymerase chain reaction; Q = question.
[a] Study patients were selected from the general population, but selection was not specifically limited to low-risk, asymptomatic individuals, or those with unknown and/or untreated hepatitis C virus (HCV) infection.
[b] Included only men who have sex with men.
[c] Included only elderly patients.
[d] While HCV screening was offered to any willing volunteers, a focused approach was taken toward those with visible tattoos and those from Thailand, Vietnam, and Laos. However, these factors were not population exclusion criteria for this review question.
[e] Majority of included patients had active HCV infection, as confirmed by an RNA test, suggesting that the description of the study population as "patients at low risk for Hepatitis C infection"[80] may not have been accurate, and that this patient group may not be applicable to a low-risk, asymptomatic, general population for a screening program.
[f] Some children included; the mean and median age were greater than 18 years, but it cannot be confirmed whether the study population was at least 80% 18-years-old and older.
[g] Clinical condition of patients not specified, although it is implied that patients were not suspected of having HCV infection, as "leftover" blood from other tests was evaluated.
[h] Patients were tested for HCV twice; those who agreed to provide a second blood sample may be systematically different than the entire study population at enrollment. Repeated screening to determine HCV incidence may not reflect the screening strategy of interest for this review.
[i] Results reported at a threshold designed to give as few positive results as possible since blood donors were assumed to be Ag-negative; this may overestimate test performance. It is unclear whether the provisional cut-off used in this study is standard or recommended.
[j] Study conducted in a tropical, malaria-endemic country where there may be a high false-positive rate on HCV enzyme immunoassays.

# Appendix 9: Study Results

## Table 17: Outcomes for the Frequency of Harms From Screening for HCV Infection (Q2)

| First Author (Year) | Over-diagnosis | Over-treatment | False-Positives | False-Negatives | Harms of Follow-Up Tests (Including Biopsy) |
|---|---|---|---|---|---|
| Groom (2008)[4] | NR | NR | NR | NR | 0.19%[a] |

HCV = hepatitis C virus; NR = not reported; Q = question.
[a] One person out of 520 viremic participants (0.19%) was hospitalized for one night for pain control following liver biopsy.

## Table 18: Outcomes for the Cost-Effectiveness of Screening for Chronic HCV Monoinfection (Q3)

| First Author (Year) | Group | ICER ($/QALY) | |
|---|---|---|---|
| | | Age 25 to 64 | Age 45 to 64 |
| Wong (2015)[35] | Intervention (Tx1): Screening plus PR (G1 – 6) | $38,117 | $34,359 |
| | Comparator: No screening (G1 – 6) | $0 | $0 |
| | Comparator (Tx2): Screening plus: simeprevir + PR (G1), sofosbuvir + ribavirin (G2 or G3), PR (G4 or G5 or G6) | $42,398 | $44,034 |
| | Comparator (Tx3): Screening plus: interferon-free DAA (G1), sofosbuvir + ribavirin (G2 or G3), PR (G4 or G5 or G6) | $34,783 | $35,562 |

DAA = direct-acting antiviral agent; G = genotype; ICER = incremental cost-effectiveness ratio; PR = pegylated interferon plus ribavirin; Q = question; QALY = quality-adjusted life-year; Tx = treatment.

### Willingness to be screened for HCV (Q4)

Six of the included studies reported numerical data regarding participant willingness to be screened for HCV; one study[58] reported acceptance of screening that was subsequently conducted during the study, and five studies[59,63,64,68,69] reported participants' hypothetical acceptance of future screening. Among participants surveyed about hypothetical willingness to be screened, the majority (62% to 97%) across populations of HCV risk levels reported that they support universal, automatic HCV testing at the hospital[64] or that they would accept an HCV test if it were offered to them.[59,63,68,69] Patients from a high-risk urban population perceived a lower rate of acceptance (86%) among other members of their community.[63] One study that evaluated HCV infection knowledge and prevalence in baby boomers reported that 42% of eligible patients approached agreed to participate in the study, and of those 90% also agreed to and underwent testing for HCV.[58] Additional details are provided in Table 19.

## Table 19: Willingness to Be Screened for HCV (Q4)

| Study (Year), Country | Population | Hypothetical or Actual Acceptance of Screening |
|---|---|---|
| Allison et al. (2016), US[58] | Emergency department patients born 1945 to 1965 | 383/427 (90%) of study participants accepted HCV screening and a structured interview by questionnaire about HCV knowledge;<br>44/427 (10%) accepted interview alone |
| Myers et al. (2015), Canada[59] | Patients attending colon cancer screening centre (majority born 1945 to 1965) | 903/1003 (90%) would accept HCV screening;<br>6/903 (0.7%) would accept blood-based testing, only;<br>46/903 (5.1%) would accept saliva-based testing, only;<br>851/903 (94.2%) would accept either blood- or saliva-based testing |
| Norton et al. (2014), US[63] | High-risk urban population accessing homeless shelters, drug rehabilitation centres, and a community drop-in centre | 97% would accept a free HCV test, if offered;<br>90% would want testing even if treatment were not possible;<br>86% think others in the community would accept free screening |
| Coffin et al. (2011), US[64] | Outpatients at hospital clinics unrelated to HCV | 168/200 (86.2%) would accept automatic hospital testing of all blood for HCV;<br>67/200 (34.7%) would accept automatic HCV screening without someone talking to them about the test first |
| Sharp et al. (2007), UK[68] | Females attending a family planning and sexual health clinic | 598/964 (62%) would accept an HCV test in the FPC;<br>231/964 (24%) were undecided about acceptance of an HCV test in the FPC |
| Vallabhaneni et al. (2006), US[69] | Inmates | 139/153 (91%) would accept HCV screening in prison;<br>4/153 (3%) undecided about acceptance of HCV screening in prison |

FPC = family planning clinic; HCV = hepatitis C virus; Q = question.

## Table 20: Clinical Validity Results for Screening With Antibody Tests (Q5a)

| First Author (Year), Study Population | | Diagnostic Test | | Total | Ab+ With Active Infection of Total Ab+ (%) | Ab– Without Active Infection of Total Ab– (%) |
|---|---|---|---|---|---|---|
| **Ortho HCV version 3.0 ELISA** | | | | | | |
| Dalgard 2003,[86] general population | | PCR | | | 72.1 | NR |
| | | **RNA+** | **RNA–** | | | |
| | **Ab+** | 62 | 24 | 86 | | |
| | **Ab–** | NR | NR | 11,370 | | |
| | | | | 11,456 | | |
| Alberti 2002,[88] general population | | Amplicor HCV Monitor | | | 73.3 | NR |
| | | **RNA+** | **RNA–** | | | |
| | **Ab+** | 85 | 31 | 116 | | |
| | **Ab–** | NR | NR | 4,704 | | |
| | | | | 4,820 | | |
| Kondili 2002,[89] general population | | Cobas Amplicor HCV Test 2.0 | | | 87.5 | NR |
| | | **RNA+** | **RNA–** | | | |
| | **Ab+** | 28 | 4 | 32 | | |
| | **Ab–** | NR | NR | 2000 | | |
| | | | | 2032 | | |
| Maio 2000,[91] general population | | RT-PCR | | | 46.7 | NR |
| | | **RNA+** | **RNA–** | | | |
| | **Ab+** | 43 | 49 | 92 | | |
| | **Ab–** | NR | NR | 396 | | |
| | | | | 488 | | |
| Lucas 1999,[92] blood donors | | Amplicor PCR test | | | 0 | NR |
| | | **RNA+** | **RNA–** | | | |
| | **Ab+** | 0 | 36 | 36 | | |
| | **Ab–** | NR | NR | 562 | | |
| | | | | 598 | | |
| Guadagnino 1997,[93] general population | | RT-PCR | | | 75.9 | NR |
| | | **RNA+** | **RNA–** | | | |
| | **Ab+** | 148 | 47 | 195 | | |
| | **Ab–** | NR | NR | 1,157 | | |
| | | | | 1,352 | | |
| Vrielink 1997,[94] blood donors | | RT-PCR | | | 3.9 | NR |
| | | **RNA+** | **RNA–** | | | |
| | **Ab+** | 15 | 372 | 387 | | |
| | **Ab–** | NR | NR | 261,703 | | |
| | | | | 262,090 | | |
| **ARCHITECT Anti-HCV CMIA** | | | | | | |
| Blaxhult 2014,[71] MSM at STI clinic | | Cobas TaqMan RT-PCR | | | 33.3 | NR |
| | | **RNA+** | **RNA–** | | | |
| | **Ab+** | 2 | 4 | 6 | | |
| | **Ab–** | NR | NR | 1,002 | | |

## Table 20: Clinical Validity Results for Screening With Antibody Tests (Q5a)

| First Author (Year), Study Population | | Diagnostic Test | | Total | Ab+ With Active Infection of Total Ab+ (%) | Ab– Without Active Infection of Total Ab– (%) |
|---|---|---|---|---|---|---|
| | | | | 1,008 | | |
| Sommese 2014,[72] blood donors | | Cobas TaqScreen MPX RT-PCR | | | 28.0 | NR |
| | | **RNA+** | **RNA–** | | | |
| | **Ab+** | 7 | 18 | 25 | | |
| | **Ab–** | NR | NR | 815 | | |
| | | | | 840 | | |
| | | Cobas TaqScreen MPX RT-PCR | | | 38.9 | NR |
| | | **RNA+** | **RNA–** | | | |
| | **Ab+**[a] | 7 | 11 | 18 | | |
| | **Ab–** | NR | NR | 822 | | |
| | | | | 840 | | |
| Sommese 2014,[73] blood donors | | Cobas TaqScreen MPX RT-PCR | | | 10.1 | NR |
| | | **RNA+** | **RNA–** | | | |
| | **Ab+** | 9 | 80 | 89 | | |
| | **Ab–** | NR | NR | 17,823 | | |
| | | | | 17,912 | | |
| Zeba 2014,[76] blood donors | | GeneAmp RT-PCR | | | 33.0 | NR |
| | | **RNA+** | **RNA–** | | | |
| | **Ab+**[b] | 32 | 65 | 97 | | |
| | **Ab–** | NR | NR | 2,103 | | |
| | | | | 2,200 | | |
| Kesli 2011,[80] microbiology department patients | | Rotor-Gene 6000 RT-PCR | | | 80.3 | 73.7 |
| | | **RNA+** | **RNA–** | | | |
| | **Ab+** | 155 | 38 | 193 | | |
| | **Ab–** | 5 | 14 | 19 | | |
| | **Total** | 160 | 52 | 212 | | |
| Kesli 2009,[81] microbiology department patients | | Rotor-Gene 6000 RT-PCR | | | 75.6 | NR |
| | | **RNA+** | **RNA–** | | | |
| | **Ab+** | 65 | 21 | 86 | | |
| | **Ab–** | NR | NR | 7,070 | | |
| | | | | 7,156 | | |
| **VITROS Anti-HCV CLIA** | | | | | | |
| Martins 2013,[78] general population (elderly) | | Cobas Amplicor HCV Test 2.0 | | | 77.8 | NR |
| | | **RNA+** | **RNA–** | | | |
| | **Ab+** | 14 | 4 | 18 | | |
| | **Ab–** | NR | NR | 802 | | |
| | | | | 820 | | |
| Woo 2013,[79] general population (community fair) | | Cobas AmpliPrep | | | 0 | NR |
| | | **RNA+** | **RNA–** | | | |
| | **Ab+** | 0 | 1 | 1 | | |
| | **Ab–** | NR | NR | 230 | | |

## Table 20: Clinical Validity Results for Screening With Antibody Tests (Q5a)

| First Author (Year), Study Population | | Diagnostic Test | | Total | Ab+ With Active Infection of Total Ab+ (%) | Ab– Without Active Infection of Total Ab– (%) |
|---|---|---|---|---|---|---|
| | | | | 231 | | |
| **Cobas e411 Anti-HCV ECLIA** | | | | | | |
| Sommese 2014,[72] blood donors | | Cobas TaqScreen MPX RT-PCR | | | 36.8 | NR |
| | | **RNA+** | **RNA–** | | | |
| | **Ab+** | 7 | 12 | 19 | | |
| | **Ab–** | NR | NR | 821 | | |
| | | | | 840 | | |
| | | Cobas TaqScreen MPX RT-PCR | | | 41.2 | NR |
| | | **RNA+** | **RNA–** | | | |
| | **Ab+**[a] | 7 | 10 | 17 | | |
| | **Ab–** | NR | NR | 823 | | |
| | | | | 840 | | |
| **Cobas e601 Anti-HCV ECLIA** | | | | | | |
| Kesli 2009,[81] microbiology department patients | | Rotor-Gene 6000 RT-PCR | | | 47.8 | NR |
| | | **RNA+** | **RNA–** | | | |
| | **Ab+** | 65 | 71 | 136 | | |
| | **Ab–** | NR | NR | 7,020 | | |
| | | | | 7,156 | | |
| **Murex anti-HCV version 4.0 ELISA** | | | | | | |
| Valois 2014,[74] blood donors | | RT-PCR | | | 72.6 | NR |
| | | **RNA+** | **RNA–** | | | |
| | **Ab+** | 106 | 40 | 146 | | |
| | **Ab–** | NR | NR | 13,626 | | |
| | | | | 13,772 | | |
| Baha (2013),[75] General Population | | Cobas AmpliPrep/Cobas Amplicor | | | 71.0 | NR |
| | | **RNA+** | **RNA–** | | | |
| | **Ab+**[c] | 462 | 189 | 651 | | |
| | **Ab–** | NR | NR | 40,618 | | |
| | | | | 41,269 | | |
| **Murex Anti-HCV ELISA, Third Generation** | | | | | | |
| Zervou (2003),[87] Blood Donors | | RT-PCR and DEIA | | | 17.1 | NR |
| | | **RNA+** | **RNA–** | | | |
| | **Ab+** | 7 | 34 | 41 | | |
| | **Ab–** | NR | NR | 6,655 | | |
| | | | | 6,696 | | |
| **Biochain Anti-HCV ELISA**[d] | | | | | | |
| Lyons (2016),[70] ED patients | | RT-PCR With SYBR Green Ultra-Fast Program | | | 80.5 | 99.7 |
| | | **RNA+** | **RNA–** | | | |
| | **Ab+** | 103 | 25 | 128 | | |
| | **Ab–** | 2 | 794 | 796 | | |

## Table 20: Clinical Validity Results for Screening With Antibody Tests (Q5a)

| First Author (Year), Study Population | | Diagnostic Test | | Total | Ab+ With Active Infection of Total Ab+ (%) | Ab– Without Active Infection of Total Ab– (%) |
|---|---|---|---|---|---|---|
| | **Total** | 105 | 819 | 924 | | |
| **Wantai Core Anti-HCV ELISA and Kehua Core Anti-HCV ELISA, third Generation** | | | | | | |
| Li (2013),[77] General Population | | Amplicor HCV RT-PCR | | | 37.3 | NR |
| | | **RNA+** | **RNA–** | | | |
| | **Ab+** | 44 | 74 | 118 | | |
| | **Ab–** | NR | NR | 7,071 | | |
| | | | | 7,189 | | |
| **DiaSorin anti-HCV ELISA, Third Generation** | | | | | | |
| Rashdan (2008),[82] Blood Donors | | PCR | | | 89.7 | NR |
| | | **RNA+** | **RNA–** | | | |
| | **Ab+** | 26 | 3 | 29 | | |
| | **Ab–** | NR | NR | 14,207 | | |
| | | | | 14,236 | | |
| **INNOTEST HCV Ab III ELISA** | | | | | | |
| Reis (2008),[83] General Population | | RT-PCR | | | 0 | NR |
| | | **RNA+** | **RNA–** | | | |
| | **Ab+** | 0 | 6 | 6 | | |
| | **Ab–** | NR | NR | 1,001 | | |
| | | | | 1,007 | | |
| | | RT-PCR | | | 0 | NR |
| | | **RNA+** | **RNA–** | | | |
| | **Ab+**[a] | 0 | 2 | 2 | | |
| | **Ab–** | NR | NR | 1,005 | | |
| | | | | 1,007 | | |
| **Bioelisa HCV 4.0 ELISA, AxSYM HCV Version 3.0 MEIA, and INNO-LIA Immunoblot** | | | | | | |
| Slavenburg (2008),[84] Clinical Lab Blood Samples | | Cobas TaqMan RT-PCR | | | 50 | NR |
| | | **RNA+** | **RNA–** | | | |
| | **Ab+** | 2 | 2 | 4 | | |
| | **Ab–** | NR | NR | 2,196 | | |
| | | | | 2,200 | | |

Ab = antibody; CLIA = chemiluminescent immunoassay; CMIA = chemiluminescent microparticle immunoassay; DEIA = DNA enzyme immunoassay; ECLIA = electrochemiluminescent immunoassay; ECLIA = electrochemiluminescent immunoassay; ; ED = emergency department; ELISA = enzyme-linked immunosorbent assay; HCV = hepatitis C virus; MEIA = microparticle enzyme immunoassay; MSM = men who have sex with men; NR = not reported; PCR = polymerase chain reaction; Q = question; RNA = ribonucleic acid; RT-PCR = reverse transcription polymerase chain reaction; STI = sexually transmitted infection.

[a] Samples confirmed with INNO-LIA.

[b] Samples considered Ab+ if reactive on both the initial screening test (ARCHITECT) and the second Ab test (Bio-Rad ELISA).

[c] Samples considered Ab+ if reactive on both the initial screening test (Murex) and the second Ab test (AxSYM HCV MEIA).

[d] Generation not specified but only the third generation test is currently in production.

## Table 21: Clinical Validity Results for Screening With Antigen Tests (Q5b)

| First Author (Year) | | Diagnostic Test | | Total | Ag+ With Active Infection of Total Ag+ (%) | Ag– Without Active Infection of Total Ag– (%) |
|---|---|---|---|---|---|---|
| **ARCHITECT HCV Antigen CMIA** | | | | | | |
| Kesli (2011),[80] Microbiology Department Patients | | Rotor-Gene 6000 RT-PCR | | | 100 | 89.7 |
| | | **RNA+** | **RNA–** | | | |
| | **Ag+** | 154 | 0 | 154 | | |
| | **Ag–** | 6 | 52 | 58 | | |
| | **Total** | 160 | 52 | 212 | | |
| **PRISM HCV Core Antigen CLIA** | | | | | | |
| Muerhoff (2002),[90] Blood Donors | | RT-PCR | | | 0 | NR |
| | | **RNA+** | **RNA–** | | | |
| | **Ag+** | 0 | 1 | 1 | | |
| | **Ag–** | NR | NR | 1,003 | | |
| | | | | 1,004 | | |
| **Ortho HCV Core Antigen ELISA** | | | | | | |
| Letowska (2004),[85] Blood Donors | | Cobas Amplicor HCV Test 2.0 | | | 20.2 | NR |
| | | **RNA+** | **RNA–** | | | |
| | **Ag+** | 25 | 99 | 124 | | |
| | **Ag–** | NR | NR | 133,155 | | |
| | | | | 133,279 | | |
| Icardi (2001),[24] Blood Donors | | Cobas Amplicor HCV Test 2.0 | | | 100 | NR |
| | | **RNA+** | **RNA–** | | | |
| | **Ag+** | 2 | 0 | 2 | | |
| | **Ag–** | NR | NR | 2,584 | | |
| | | | | 2,586 | | |
| Icardi (2001),[24] General Population | | Cobas Amplicor HCV Test 2.0 | | | Not Evaluable | NR |
| | | **RNA+** | **RNA–** | | | |
| | **Ag+** | 0 | 0 | 0 | | |
| | **Ag–** | NR | NR | 500 | | |
| | | | | 500 | | |

Ag = antigen; CLIA = chemiluminescent immunoassay; CMIA = chemiluminescent microparticle immunoassay; ELISA = enzyme-linked immunosorbent assay; HCV = hepatitis C virus; NR = not reported; Q = question; RNA = ribonucleic acid; RT-PCR = reverse transcription polymerase chain reaction.

# Appendix 10: GRADE Tables

## Table 22: GRADE Assessment on the Clinical Effectiveness of Screening for HCV Infection (Q1)

| **Setting**: Primary care or other settings generalizable to primary care; other settings in which screening is commonly performed (e.g., emergency department, urgent care units) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Quality Assessment** | | | | | | | **Number of Patients** | | **Effect** | **Overall Quality of Evidence** |
| **Number of Studies** | **Study Design** | **Risk of Bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Publication Bias** | **Screening for HCV Infection** | **No Screening** | **Relative Mean Change Between Groups** | |
| **Mortality due to HCV infection:** No evidence identified | | | | | | | | | | |
| **Morbidity (including compensated or decompensated cirrhosis) due to HCV infection:** No evidence identified | | | | | | | | | | |
| **Hepatocellular carcinoma:** No evidence identified | | | | | | | | | | |
| **Liver transplantation:** No evidence identified | | | | | | | | | | |
| **Quality of life:** No evidence identified | | | | | | | | | | |
| **HCV transmission:** No evidence identified | | | | | | | | | | |
| **Virologic response:** No evidence identified | | | | | | | | | | |
| **Behavioural changes to improve health outcomes:** No evidence identified | | | | | | | | | | |
| **Histological changes:** No evidence identified | | | | | | | | | | |

GRADE = Grading of Recommendations Assessment, Development and Evaluation; HCV = hepatitis C virus; Q = question.

## Table 23: GRADE Assessment on the Frequency of Harms of Screening for HCV Infection (Q2)

| **Setting**: Primary care or other settings generalizable to primary care; other settings in which screening is commonly performed (e.g., emergency department, urgent care units) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Quality Assessment** | | | | | | | **Study Event Rates** | | **Effect** | | **Overall Quality of Evidence** |
| **Number of Studies** | **Study Design** | **Risk of Bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Publication Bias** | **Screening for HCV Infection** | **No Screening** | **Relative (95% CI)** | **Absolute (95% CI)** | |
| **Over-diagnosis:** No evidence identified | | | | | | | | | | | |
| **Over-treatment:** No evidence identified | | | | | | | | | | | |
| **False-positives:** No evidence identified | | | | | | | | | | | |
| **False-negatives:** No evidence identified | | | | | | | | | | | |
| **Harms of follow-up tests (including biopsy)**: Not evaluable[a] | | | | | | | | | | | |
| **Abuse or violence:** No evidence identified | | | | | | | | | | | |
| **Anxiety:** No evidence identified | | | | | | | | | | | |

CI = confidence interval; GRADE = Grading of Recommendations Assessment, Development and Evaluation; HCV = hepatitis C virus; Q = question.
[a] Evidence identified from one non-comparative study.

## Table 24: CERQual Assessment of the Evidence on the Preferences and Values Regarding the Decision to Be Screened for HCV Infection (Q4)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Objective:** To identify, appraise, and synthesize descriptive and mixed-methods research evidence on the preferences and values regarding the decision to be screened for HCV infection | | | | | | | |
| **Perspective:** Experiences and attitudes of asymptomatic, non-pregnant, treatment-naive adults with unknown liver enzyme values | | | | | | | |
| **Included interventions:** Any screening method for HCV infection in primary care, other settings generalizable to primary care, or other settings in which screening is commonly performed (e.g., emergency department, urgent care units) | | | | | | | |
| **Review Finding** | **Studies Contributing to the Review Finding** | **Assessment of Methodological Limitations** | **Assessment of Relevance** | **Assessment of Coherence** | **Assessment of Adequacy** | **Overall CERQual Assessment of Confidence** | **Explanation of Judgment** |
| Knowledge of and desire to know HCV status, level of perceived personal risk, and knowledge of HCV influence the decision to be screened. | Allison et al. (2016),[58] Barocas et al. (2014),[61] Norton et al. (2014),[63] Coffin et al. (2011),[64] Zuure et al. (2011),[65] Day et al. (2008),[66] Sharp et al. (2007),[68] Vallabhaneni et al. (2006)[69] | Moderate methodological limitations (4 studies with minor and 4 studies with moderate methodological limitations)[a] | Minor concerns about relevance (studies of high risk, high prevalence, and general populations, mostly conducted in settings where screening is commonly performed) | Minor concerns about coherence (data reasonably consistent within and across studies) | Minor concerns about adequacy (8 studies that offered moderately rich data overall) | Moderate confidence | The overall assessment of confidence in this finding was moderate because of minor concerns regarding relevance, coherence, and adequacy, and moderate concerns regarding methodological limitations. |
| People consider the implications for and availability of management for HCV when deliberating about screening. | Norton et al. (2014),[63] Coffin et al. (2011),[64] Zuure et al. (2011),[65] Day et al. (2008)[66] | Minor methodological limitations (3 studies with minor and 1 study with moderate methodological | Moderate concerns about relevance (uncertain relevance, as it is unclear whether individuals from high-prevalence | Minor concerns about coherence (data consistent within and across studies) | Minor concerns about adequacy (4 studies that offered moderately rich data overall) | Moderate confidence | The overall assessment of confidence in this finding was moderate because of minor concerns regarding |

## Table 24: CERQual Assessment of the Evidence on the Preferences and Values Regarding the Decision to Be Screened for HCV Infection (Q4)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Objective:** To identify, appraise, and synthesize descriptive and mixed-methods research evidence on the preferences and values regarding the decision to be screened for HCV infection | | | | | | | |
| **Perspective:** Experiences and attitudes of asymptomatic, non-pregnant, treatment-naive adults with unknown liver enzyme values | | | | | | | |
| **Included interventions:** Any screening method for HCV infection in primary care, other settings generalizable to primary care, or other settings in which screening is commonly performed (e.g., emergency department, urgent care units) | | | | | | | |
| **Review Finding** | **Studies Contributing to the Review Finding** | **Assessment of Methodological Limitations** | **Assessment of Relevance** | **Assessment of Coherence** | **Assessment of Adequacy** | **Overall CERQual Assessment of Confidence** | **Explanation of Judgment** |
| | | limitations)[b] | groups were well-represented)[c] | | | | methodological limitations, coherence, and adequacy, and moderate concerns regarding relevance. |
| Decisions about HCV screening are influenced by psychological and interpersonal contexts such as fear, embarrassment, denial, interest in personal health, concern for others, and relationships with others. | Barocas et al. (2014),[61] Norton et al. (2014),[63] Coffin et al. (2011),[64] Zuure et al. (2011),[65] Day et al. (2008),[66] Khaw et al. (2007)[67] Sharp et al. (2007),[68] | Moderate methodological limitations (5 studies with minor and 2 studies with moderate methodological limitations)[d] | Moderate concerns about relevance (uncertain relevance, as it is unclear whether individuals from high-prevalence groups were well-represented)[c] | Minor concerns about coherence (consistent data across studies) | Minor concerns with adequacy (3 studies[61,65,67] offered particularly rich data) | Moderate confidence | The overall assessment of confidence in this finding was moderate because of minor concerns about coherence and adequacy, and moderate concerns about methodological limitations and relevance. |

## Table 24: CERQual Assessment of the Evidence on the Preferences and Values Regarding the Decision to Be Screened for HCV Infection (Q4)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Objective:** To identify, appraise, and synthesize descriptive and mixed-methods research evidence on the preferences and values regarding the decision to be screened for HCV infection | | | | | | | |
| **Perspective:** Experiences and attitudes of asymptomatic, non-pregnant, treatment-naive adults with unknown liver enzyme values | | | | | | | |
| **Included interventions:** Any screening method for HCV infection in primary care, other settings generalizable to primary care, or other settings in which screening is commonly performed (e.g., emergency department, urgent care units) | | | | | | | |
| **Review Finding** | **Studies Contributing to the Review Finding** | **Assessment of Methodological Limitations** | **Assessment of Relevance** | **Assessment of Coherence** | **Assessment of Adequacy** | **Overall CERQual Assessment of Confidence** | **Explanation of Judgment** |
| Preferences around the implementation of screening include views about consent and initiators of testing, clinical setting of screening, test methods, and delivery of test information and results. | Allison et al. (2016),[58] Myers et al. (2015),[59] Barocas et al. (2014),[61] Hayes et al. (2014),[62] Coffin et al. (2011),[64] Zuure et al. (2011),[65] Day et al.(2008),[66] Khaw et al. (2007)[67] | Moderate methodological limitations (6 studies with minor and 2 studies with major methodological limitations)[e] | Moderate concerns about relevance (indirect relevance because of the setting in some studies)[f] | Moderate concerns about coherence (some inconsistency across studies regarding the elements of implementation that were discussed and which factors were considered important) | Major concerns with adequacy (8 studies provided generally thin data)[g] | Low confidence | The overall assessment of confidence in this finding was low because of some moderate concerns about methodological limitations, relevance, and coherence, and major concerns about adequacy. |
| PWID and inmates experience unique barriers to HCV screening related to stigma and access to health care. | Barocas et al. (2014),[61] Day et al. (2008),[66] Khaw et al. (2007)[67] | Major methodological limitations (1 study with minor and 2 studies with major methodological limitations)[h] | Moderate concerns about relevance (partial relevance to the target population of the research question) | Minor concerns about coherence (data were reasonably consistent across studies) | Moderate concerns about adequacy (few studies identified with relatively rich data) | Low confidence | The overall assessment of confidence in this finding was low because of minor concerns about coherence, moderate concerns about relevance and |

## Table 24: CERQual Assessment of the Evidence on the Preferences and Values Regarding the Decision to Be Screened for HCV Infection (Q4)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Objective:** To identify, appraise, and synthesize descriptive and mixed-methods research evidence on the preferences and values regarding the decision to be screened for HCV infection | | | | | | | |
| **Perspective:** Experiences and attitudes of asymptomatic, non-pregnant, treatment-naive adults with unknown liver enzyme values | | | | | | | |
| **Included interventions:** Any screening method for HCV infection in primary care, other settings generalizable to primary care, or other settings in which screening is commonly performed (e.g., emergency department, urgent care units) | | | | | | | |
| **Review Finding** | **Studies Contributing to the Review Finding** | **Assessment of Methodological Limitations** | **Assessment of Relevance** | **Assessment of Coherence** | **Assessment of Adequacy** | **Overall CERQual Assessment of Confidence** | **Explanation of Judgment** |
| | | | | | | | adequacy, and major concerns about methodological limitations. |

CERQual = Confidence in the Evidence from Reviews of Qualitative Research; HCV = hepatitis C virus; PWID = people who inject drugs; Q = question.
[a] The sub-finding regarding the association between knowledge of HCV and willingness to screen is particularly impacted by studies with problematic sampling methods and risk of social desirability bias that could overestimate acceptance of screening. Among other sub-findings, there was relatively equal distribution of studies, with minor and moderate methodological limitations.
[b] The overall trend observed regarding the desire for treatment after receiving a positive test result is likely reasonable, but the proportion of people with this view, as reported in one study (99%),[63] was likely inflated due to selection and social desirability biases in the study conduct.
[c] Studies contributing to this finding included high-risk participants and those from a general population; one study[65] included participants from high-prevalence countries, but no studies specifically addressed a high-prevalence birth cohort.
[d] Methodological limitations in two studies[63,67] related to concerns regarding participant selection, potential social desirability bias, and insufficient reporting on the interview process and analysis strategy.
[e] Major methodological limitations in two studies[58,67] regarding the insufficient reporting of participant selection, interview questions and responses, and analysis methods reduced the overall methodological quality of the body of evidence contributing to this finding.
[f] Studies conducted in non-primary care settings such as prisons and community-based resource centres contributed substantive data to this finding and may reflect implementation preferences that are not relevant to the health care setting of interest for this review.
[g] Because of the narrow scope of included studies, data were not adequately rich regarding situations in which reported preferences will be important.
[h] Major methodological limitations in two studies[66,67] related to participant selection, risk of social desirability bias, and the use of a researcher-defined questionnaire that does not allow for participants' expressions in their own words reduce confidence in the findings.

## Table 25: GRADE Assessment of the Evidence for the Clinical Validity of Screening With Antibody Tests (Q5a)

**Setting**: Primary care or other settings generalizable to primary care; other settings in which screening is commonly performed (e.g., emergency department, urgent care units)

| Outcome | Number of Studies and Patients | Study Design | Factors That May Decrease the Quality of Evidence | | | | | Range of Reported Values (%) | Quality of Evidence |
|---|---|---|---|---|---|---|---|---|---|
| | | | Risk of Bias | Indirectness | Inconsistency | Imprecision | Publication Bias | | |
| **Ab+RNA+ of total Ab+** | 23 studies, N = 400,508 | Cross-sectional | Serious[a] | Not serious | Serious[b] | Not applicable[c] | Undetected | 0 to 89.7 | **Low** |
| **Ab–RNA+ of total Ab–** | 2 studies, N = 1,136 | Cross-sectional | Serious[d] | Not serious | Serious[b] | Not applicable[c] | Undetected | 0.3 to 26.3 | **Low** |
| **Ab–RNA– of total Ab–** | 2 studies, N = 1,136 | Cross-sectional | Serious[d] | Not serious | Serious[b] | Not applicable[c] | Undetected | 73.7 to 99.7 | **Low** |
| **Ab+RNA– of total Ab+** | 23 studies, N = 400,508 | Cross-sectional | Serious[a] | Not serious | Serious[b] | Not applicable[c] | Undetected | 10.3 to 100 | **Low** |

Ab+ = antibody-positive; Ab- = antibody-negative; GRADE = Grading of Recommendations Asssessment, Development and Evaluation; HCV = hepatitis C virus; Q = question; RNA+ = ribonucleic acid-positive; RNA- = ribonucleic acid-negative.

[a] Due to unclear risk of bias related to patient selection and/or test methods in approximately one-third of studies.

[b] Due to wide range of reported values for the outcomes that cannot clearly be explained by a specific source of heterogeneity.

[c] Imprecision cannot be assessed, as results were not reported as a point estimate with a 95% confidence interval, the population contributing to this outcome was large, and there was a large range in proportions reported for this outcome.

[d] Due to unclear risk of bias related to patient selection in one study.[80]

## Table 26: GRADE Assessment of the Evidence for the Clinical Validity of Screening With Antigen Tests (Q5b)

**Setting**: Primary care or other settings generalizable to primary care; other settings in which screening is commonly performed (e.g., emergency department, urgent care units)

| Outcome | Number of Studies and Patients | Study Design | Factors That May Decrease Quality of Evidence | | | | | Range of Reported Values (%) | Quality of Evidence |
|---|---|---|---|---|---|---|---|---|---|
| | | | Risk of Bias | Indirectness | Inconsistency | Imprecision | Publication Bias | | |
| **Ag+RNA+ of total Ag+** | 4 studies, N = 137,581 | Cross-sectional | Serious[a] | Not serious | Serious[b] | Not applicable[c] | Undetected | 0 to 100 | **Low** |
| **Ag–RNA+ of total Ag–** | 1 study, N = 212 | Cross-sectional | Serious[d] | Not serious | Not serious[e] | Serious[f] | Undetected | 89.7 | **Low** |
| **Ag–RNA– of total Ag–** | 1 study, N = 212 | Cross-sectional | Serious[d] | Not serious | Not serious[e] | Serious[f] | Undetected | 10.3 | **Low** |
| **Ag+RNA– of total Ag+** | 4 studies, N = 137,581 | Cross-sectional | Serious[a] | Not serious | Serious[b] | Not applicable[c] | Undetected | 0 to 100 | **Low** |

Ag+ = antigen-positive; Ag- = antigen-negative; GRADE = Grading of Recommendations Asssessment, Development and Evaluation; Q = question; RNA+ = ribonucleic acid-positive; RNA- = ribonucleic acid-negative.

[a] Due to unclear patient selection methods in one study[80] and a high risk of bias related to the screening test in one study.[90]

[b] Due to a wide range of reported values for the outcomes that cannot clearly be explained by a specific source of heterogeneity.

[c] Imprecision cannot be assessed, as results were not reported as a point estimate with a 95% confidence interval.

[d] Due to unclear patient selection methods.[80]

[e] A single study provided data for the outcome, therefore inconsistency was not identified.

[f] Due to few events reported for this outcome.