UK National Screening Committee

Antenatal screening for hepatitis C virus

External review against programme appraisal criteria for the UK National Screening Committee

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The UK National Screening Committee secretariat is hosted by Public Health England.

About the UK National Screening Committee (UK NSC)

The UK NSC advises ministers and the NHS in the 4 UK countries about all aspects of population screening and supports implementation of screening programmes.
Conditions are reviewed against evidence review criteria according to the UK NSC's evidence review process.

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Plain English summary

Hepatitis C is a virus that spreads through contact with infected blood or other body fluids. This could be during a blood transfusion, tattooing, body piercing or when injecting drugs. Hepatitis C is a major global health problem affecting 2% to 3% of the world's population.

People can live with hepatitis C for many years without any symptoms. About 20% of adults with ongoing infection develop liver cirrhosis. Between 1% and 5% develop a liver cancer. Hepatitis C in pregnancy can increase the risk of pregnancy complications and miscarriage.

The main cause of hepatitis C infection in children is transfer of the virus from mother to child. In about 20% of these children the infection clears without treatment. In 80% of children the infection continues into adulthood.

This document looks at new evidence about screening pregnant women for hepatitis C published up to February 2018. A national screening programme would aim to identify pregnant women with hepatitis C and reduce the risk of the virus being passed to the child.

The UK National Screening Committee (UK NSC) published its last review in 2011. This recommended against introducing a UK screening programme for hepatitis C in pregnant women. The last review found a lack of options to manage pregnant women with hepatitis C and their children. The last review concluded that there was no advantage to detecting hepatitis C during pregnancy.

The current review looked at some key questions:

1. how many pregnant women in the UK have hepatitis C?
2. which factors increase the risk that the hepatitis C virus will be transferred from mother to child?
3. how accurate are screening tests for hepatitis C?
4. how effective are direct acting antiviral drugs in treating pregnant women and preventing the transfer of hepatitis C to their child?
5. how effective are direct acting antiviral drugs in treating children who obtain hepatitis C from their mother?

The UK NSC still cannot recommend population screening for hepatitis C in pregnant women. There was not enough new evidence to change the conclusions of the previous UK NSC review. These areas are still uncertain:

- the number of pregnant women in the UK who have hepatitis C
- the factors that increase the risk of a mother transferring the hepatitis C virus to their child
- the accuracy of screening tests for hepatitis C in pregnant women
- the effectiveness of treatments for pregnant women with hepatitis C and their children.

Executive summary

Purpose of the review

This document reviews the evidence on antenatal screening for hepatitis C virus.

Background

Hepatitis C is a blood borne virus and a major global health problem, affecting 2% to 3% of the world's population. About 85% of people infected in adulthood will develop chronic infection. There are an estimated 185,000 individuals with chronic hepatitis C in the UK.

Risk factors for hepatitis C include being born in a country with medium to high prevalence of hepatitis C virus, transfusion of infected blood, injecting drug use, tattooing and body piercing and sexual transmission. The main cause of hepatitis C infection in children is vertical transmission from mother to child.

Hepatitis C can remain asymptomatic for many years, however, about 20% of adults with chronic infection are estimated to develop liver cirrhosis and between 1% and 5% develop hepatocellular carcinoma. Without treatment, 20% of children with vertically acquired hepatitis C have been reported to clear the infection spontaneously, whereas 80% develop chronic infection that develops into adulthood. Hepatitis C in pregnancy has been associated with adverse outcomes such as higher risk of pregnancy-induced hypertension, antepartum haemorrhage, pre-eclampsia, gestational diabetes and miscarriage.

Focus of the review

The function of a national antenatal screening programme would be to identify pregnant women with hepatitis C and to reduce the risk of vertical transmission to the child or reduce the adverse consequences of hepatitis C infection in the child.

This evidence summary includes studies published up to February 2018. It considers 5 key questions relating to prevalence in the UK, risk factors for transmission, the test and the intervention:

1. what is the seroprevalence and current infection prevalence of hepatitis C virus in pregnant women in the UK?
2. which risk factors are associated with hepatitis C transmission from mother to child?
3. what is the diagnostic accuracy of second, third and fourth generation antibody tests for the detection of hepatitis C?
4. what is the reported effectiveness of direct acting antivirals (DAAs) in pregnancy for the prevention of hepatitis C vertical transmission and hepatitis C associated morbidity in pregnant women?
5. what is the reported effectiveness of direct acting antivirals (DAAs) in children with vertically acquired hepatitis C on hepatitis C associated morbidity and cure?

Recommendation under review

The current UK NSC policy is that systematic population screening for hepatitis C in pregnant women is not recommended. Previous UK NSC external reviews were published in 2003 and 2011. The most recent 2011 UK NSC review concluded that there was no advantage to identifying hepatitis C infection in pregnancy. This was due to a lack of interventions to improve the management of maternal or childhood disease and complications in the assessment of maternal disease. The 2011 review also highlighted the lack of knowledge of hepatitis C seroprevalence in the contemporary UK pregnant population.

Findings and gaps in the evidence of this review

The current review found that the volume, quality and direction of new evidence published up to February 2018 does not indicate that there have been any significant changes in the evidence base since the previous review. Areas of uncertainty relate to:

- the seroprevalence and current infection prevalence for pregnant women for the UK as a whole is unclear, as is the number of new hepatitis C cases that would be detected by screening pregnant women
- there are uncertainties about which risk factors increase the risk of vertical transmission and to what extent

- there is limited information about the performance of screening tests in pregnant women. The limited evidence available suggests a high proportion of false positives would result from screening
- there is an absence of evidence about the effectiveness of treatment with DAAs for pregnant women and children with vertically acquired hepatitis C.

Recommendations on screening

The current recommendation not to introduce a UK systematic antenatal population screening programme for hepatitis C virus should be retained.

The evidence relating to the effectiveness of treatment with DAAs for pregnant women and children with vertically acquired hepatitis C should be kept under review.

Limitations

A limitation for this review is the lack of evidence specific to the population of interest for population-based screening for hepatitis C, particularly relating to the performance of screening tests in pregnant women or the effectiveness of treatment in pregnant women or children with vertically acquired hepatitis C.

Introduction and approach

This evidence summary reviews antenatal screening for hepatitis C virus against selected UK National Screening Committee (NSC) Criteria. The function of a national antenatal screening programme would be to identify pregnant women with hepatitis C and to reduce the risk of transmission to the child or reduce the adverse consequences of hepatitis C infection in the child.

Background

Hepatitis C is a blood borne virus and a major global health problem, affecting 2% to 3% of the world's population.[1] Hepatitis C can remain asymptomatic for many years, however an estimated 85% of people infected in adulthood will develop chronic infection.[2] Of these, approximately 20% are estimated to develop liver cirrhosis and between 1% and 5% of infected adults develop hepatocellular carcinoma.[2] Hepatitis C in pregnancy has also been associated with adverse outcomes such as higher risk of pregnancy-induced hypertension, antepartum haemorrhage, pre-eclampsia, gestational diabetes and miscarriage.[1]

The number of individuals with chronically infected hepatitis C in the UK is reported to have remained stable since 2004 and was estimated at around 185,000 individuals in 2009.[1] A 2018 Public Health England (PHE) report[3] stated that there are around 160,000 people with chronically infected hepatitis C in England.

Risk factors for hepatitis C include being born in a country with medium to high hepatitis C seroprevalence[1], transfusion of infected blood, injecting drug use, other percutaneous exposures such as tattooing and body piercing and sexual transmission.[4] Since the introduction of blood screening in 1991, the main cause of hepatitis C infection in children is vertical transmission from mother to child.[1] Possible risk factors for the vertical transmission of hepatitis C include viral load and delivery factors during birth such as duration of membrane rupture and use of forceps.[1] Without treatment, 20% of children with vertically acquired hepatitis C

have been reported to clear the infection spontaneously, whereas 80% develop chronic infection that develops into adulthood.[5]

Current UK guidelines for the detection of hepatitis C involve testing high risk individuals.[1]

The last UK NSC external review in 2011 considered the evidence for population screening for hepatitis C against the UK NSC programme appraisal criteria.[2] The 2011 review reported a UK prevalence of hepatitis C in pregnant women of between 0.29% and 0.40%, citing studies from Scotland, London and Yorkshire.[2] However, a prevalence of up to 1.07% was reported in areas of high deprivation in Scotland.[2] The authors of the Scottish study[6] estimated that 24% of the infected women had been diagnosed prior to pregnancy. The 2011 review also cited a prevalence of 1.9% for hepatitis C in pregnant women with HIV, rising to 68% for women with a history of injecting drug use.[2]

The 2011 UK NSC review reported that vertical transmission of hepatitis C from mother to child occurs in 3% to 8% of cases.[2] A more recent systematic review and meta-analysis[7] reported that the risk of vertical transmission was 5.8% for children of HIV negative women and 10.8% for HIV positive women. The 2011 review stated that there was good evidence that hepatitis C viral load is a key risk factor for vertical transmission, but that the relationship between viral load and vertical transmission was not completely understood.[2] The review cited a study[8] suggesting that most children infected with hepatitis C acquire the infection during pregnancy or birth, with postpartum infection thought to be rare. The 2011 review reported that there was no evidence that preventative interventions such as elective Caesarean section might protect against transmission.[2]

The 2011 UK NSC review reported that whilst spontaneous viral clearance is possible in infected children who have not received treatment, most infected children remain positive for hepatitis C virus.[2] In a more recent systematic review, clearance of hepatitis C virus in children with transient RNA positivity occurred by a median of 15 months old.[7] A small proportion of untreated children progress to severe hepatitis or cirrhosis in childhood (eg up to 6%).[2] Other morbidities identified for infected children are fibrosis and obesity.[2]

Screening for hepatitis C typically uses serological methods to detect antibodies to the virus. These include second, third and fourth generation enzyme-linked immunosorbent assays (ELISA)*, chemiluminescent immunoassays (CLIA), electrochemiluminescent immunoassays (ECLIA), chemiluminescent microparticle immunoassays (CMIA) and microparticle enzyme immunoassays (MEIA).[1] However, antibody testing cannot distinguish between current and resolved infections.[11] Screening tests for the antibodies are followed by confirmation testing for the virus using nucleic acid amplification testing (NAAT) or antigen testing.[1] The UK Standards for Microbiology Investigation state that hepatitis C virus RNA detection using NAAT is the preferred method for confirmatory testing of ongoing infection.[1] However, it should be noted that pregnancy-related changes in hepatitis C virus RNA and alanine aminotransferase (ALT) levels can complicate the assessment of hepatitis C in pregnancy.[1] Instead of a two-step screen and diagnostic test process, it is becoming routine in many laboratories to 'reflex' test samples which are antibody positive to HCV RNA so that only patients with on-going infection are referred (personal communication).

The 2003 UK NSC review[4] discussed the performance of screening tests for hepatitis C and stated that reasonable sensitivity and specificity scores are achieved from third generation tests in some populations eg adults with chronic liver disease (98.9% and 100%). Studies with blood donors were reported to have specificities of between 96% and 99%. The 2003 review stated that there were few studies assessing test performance in general populations or pregnant women. The review did cite one small study of 521 pregnant women in Taiwan[9] which reported a sensitivity of 100% and specificity of 66% for a third generation assay. The 2003 review modelled test performance in a hypothetical UK population and found that the low UK prevalence of hepatitis C would result in low positive predictive values and therefore a high proportion of false positive tests even if a sensitivity of 100% and specificity of 96% was modelled.[4]

At the time of the 2011 UK NSC review, treatment for hepatitis C with interferon and ribavirin was contraindicated in pregnancy and no specific antiviral drugs had been approved for children less than 3 years old.[2] Combination therapy with interferon and ribavirin was standard care for older children.[2] The 2011 review cited a post-hoc multivariable analysis of

* ELISA fourth generation tests also detect hepatitis C virus core antigen

a randomised controlled trial comparing combination therapy to interferon plus placebo.[10] Non-vertical mode of acquisition was one of the factors associated with an increased probability of a sustained virologic response (SVR[†]) to treatment.[2] The odds of an SVR were 7 times greater when hepatitis C was not acquired through vertical transmission.[2]

Since the last review, direct acting antivirals (DAA) treatments have become available. These drugs disrupt viral replication and therefore infection.[11] There are different classes of DAAs, defined by their mechanism of action and therapeutic target.[11] These include second-generation NS3/NS4A protease inhibitors such as simeprevir and paritaprevir and NS5B polymerase inhibitors such as sofosbuvir and dasabuvir.[11] If DAAs are considered effective and safe to use in pregnancy they may provide a potential option for a preventative intervention in pregnancy and/or following postnatal detection and follow-up testing of an infected child.[1]

Current policy context and previous reviews

The current UK NSC policy is that systematic antenatal population screening for hepatitis C is not recommended. Two previous UK NSC reviews have been undertaken. The 2011 UK NSC review[2] considered literature published between January 2003 and September 2010 and the 2003 UK NSC review considered literature published prior to 2003.[4]

The last UK NSC review in 2011[2] concluded that there was no advantage to identifying hepatitis C infection in pregnancy due to a lack of interventions to improve the management of maternal or childhood disease and complications in the assessment of maternal disease. The 2011 review also highlighted the lack of knowledge of hepatitis C seroprevalence in the contemporary UK pregnant population.[2]

The UK NSC has recently produced a separate evidence map on the clinical and cost-effectiveness of antenatal and postnatal hepatitis C virus screening programmes, based on literature published up to January 2018.[12] The summary of this evidence map is provided as Appendix 5. This found that there have been no randomised controlled trials (RCT) or

[†] Where hepatitis C virus is not detected in the blood after treatment

observational studies comparing vertical transmission rates in screened pregnant women compared to unscreened women. There were also no RCTs or observational studies comparing clinical outcomes in screened and unscreened pregnant women and their infants. There was a similar lack of studies of postnatal screening.[12] In addition, 4 systematic reviews of economic evaluations concluded that hepatitis C virus screening in pregnancy was not cost-effective.[12]

Objectives

The aim of the current review is to update the evidence in key areas identified in the previous review. The key questions addressed in the current review were developed by the UK NSC with input from Solutions for Public Health.

The key questions and the UK NSC criteria that they relate to are presented in Table 1 below.

Table 1. Key questions for the evidence summary, and relationship to UK NSC screening criteria.

	Criterion	Key questions	Studies Included
	THE CONDITION		
1	The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.	1. What is the seroprevalence and current infection prevalence of hepatitis C virus in pregnant women in the UK?	3
		2. Which risk factors are associated with hepatitis C transmission from mother to child?	6
	THE TEST		
4	There should be a simple, safe, precise and validated screening test.	3. What is the diagnostic accuracy of second, third and fourth generation antibody tests for the detection of hepatitis C?	0
	THE INTERVENTION		
9	There should be an effective intervention for patients identified through screening, with evidence that intervention at	4. What is the reported effectiveness of direct acting antivirals	0

Criterion	Key questions	Studies Included
a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldn't be further considered.	(DAAs) in pregnancy for the prevention of hepatitis C vertical transmission and hepatitis C associated morbidity in pregnant women? 5. What is the reported effectiveness of DAAs in children with vertically acquired hepatitis C on hepatitis C associated morbidity and cure?	0

Methods

The current review was conducted by Solutions for Public Health (SPH), in keeping with the UK National Screening Committee evidence review process. Database searches were conducted on 21st February 2018 to identify studies relevant to the questions detailed in Table 1.

Eligibility for inclusion in the review

The following review process was followed:

1. each abstract was reviewed against the inclusion/ exclusion criteria by 1 reviewer. Where the applicability of the inclusion criteria was unclear from the abstract, the article was included at this stage in order to ensure that all potentially relevant studies were captured.
2. full text articles required for the full text review stage were acquired.
3. each full-text article was reviewed against the inclusion/ exclusion criteria by 1 reviewer, who determined whether the article was relevant to 1 or more of the review questions.
4. any queries at the abstract or full text stage were resolved through discussion with a second reviewer.
5. the review was quality assured by a second senior reviewer, not involved with the writing of the review in accordance with SPH's quality assurance process.

Eligibility criteria for each key question are presented in Table 2 below. For questions 1, 2, 4 and 5 only peer reviewed studies published in English between September 2010 and February 2018 were eligible for consideration in the review. For question 3, studies published between 2003 and February 2018 were eligible for consideration in the review.

A total of 815 unique references were identified and sifted by an information scientist by title and abstract for potential relevance to the review. An SPH reviewer assessed 134 titles and abstracts for further appraisal and possible inclusion in the final review.

Overall, 48 studies were identified as possibly relevant during title and abstract sifting and further assessed at full text (see Appendix 2 for study flow).

Table 2. Inclusion and exclusion criteria for the key questions.

Key question	Inclusion criteria:						Exclusion criteria:
	Population	**Target condition**	**Intervention**	**Comparator**	**Outcomes**	**Study type**	
1. What is the seroprevalence and current infection prevalence of hepatitis C virus in pregnant women in the UK?	Pregnant women in the UK	Hepatitis C virus	N/A	N/A	Seroprevalence and current infection prevalence	Cross sectional studies, cohort studies and systematic reviews of these	Case reports Case series Narrative reviews
2. Which risk factors are associated with hepatitis C transmission from mother to child?	Pregnant women positive for hepatitis C	Hepatitis C virus	Exposure: Any subgroup, characteristic or clinical or laboratory parameter related to the hepatitis C virus, the mother the child or the pregnancy and birth process evaluated for vertical transmission	Any subgroup, characteristic or clinical or laboratory parameter related to the hepatitis C virus, the mother the child or the pregnancy and birth process used as the reference categories to exposure 1	Occurrence of hepatitis C with at least one measurement at 15 months or older	Case-control studies, cohort studies and systematic reviews of these	Case reports Case series Narrative reviews

3. What is the diagnostic accuracy of second, third and fourth generation antibody tests for the detection of hepatitis C?	Pregnant women. General population if no or insufficient studies in the population of interest	Hepatitis C virus	Any 2nd to 4th generation test to detect antibodies for hepatitis C using serological methods, including ELISA, EIA, CLIA or Immunoblots	Reference standard: Any test used to detect hepatitis C RNA, eg polymerase chain reaction or NAAT	Sensitivity, specificity, PPV, NPV	Cross-sectional studies, cohort studies and systematic reviews of these Studies in randomly assigned or consecutively enrolled populations should be prioritised	Case reports Case series Case control studies Narrative reviews
4. What is the reported effectiveness of DAAs in pregnancy for the prevention of hepatitis C vertical transmission and hepatitis C associated morbidity in pregnant women?	Pregnant women	Hepatitis C virus	Direct acting antivirals	Any or none	Primary outcome: percentage of hepatitis C transmission from mother to infant Secondary outcomes: any hepatitis C related pregnancy or childbirth outcome investigated; cure rates; adverse events from treatment	RCTs, quasi-experimental studies, cohort studies, case-control studies and systematic reviews of these	Case reports Case series Narrative reviews
5. What is the reported effectiveness of DAAs in children with vertically	In order of priority: Children with vertically	Hepatitis C virus	Direct acting antivirals	In order of priority: Treatment of children after onset of	Any hepatitis C related outcome investigated	RCTs, quasi-experimental studies, cohort studies, case-control studies and systematic reviews of	Case reports Case series Narrative reviews

acquired hepatitis C on hepatitis C associated morbidity and cure?	transmitted hepatitis C Children with hepatitis C treated before the age of 5	hepatitis C symptoms Any or none	these

CLIA - Chemiluminescent Immunoassays; DAA - Direct acting antivirals; EIA - Enzyme Immunoassays; ELISA - Enzyme Linked Immunosorbent Assays; NAAT - Nucleic Acid Amplification Testing; NPV – Negative Predictive Value; PPV – Positive Predictive Value; RCT – Randomised Controlled Trial; RNA – Ribonucleic acid

Appraisal for quality/risk of bias tool

The following tools were used to assess the quality and risk of bias of each study included in the review:

- systematic reviews: Critical Appraisal Skills Programme (CASP) Systematic Review Checklist
- cohort studies: Critical Appraisal Skills Programme (CASP) Cohort Study Checklist
- prevalence studies: JBI Critical Checklist for Studies Reporting Prevalence Data.

Results of the quality assessments are presented in the summary and appraisal of individual studies in Appendix 3.

Databases/sources searched

A systematic search of 3 databases (Medline, Embase and Cochrane) was conducted on 21st February 2018 to identify studies relevant to the questions detailed in Table 1. The search strategy is presented in Appendix 1.

Question level synthesis

Criterion 1 – The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.

Question 1 – What is the seroprevalence and current infection prevalence of hepatitis C virus in pregnant women in the UK?

This question was considered by the 2011 UK NSC evidence review[2] which reported an overall prevalence for hepatitis C virus of between 0.29% and 0.40% from UK studies, but also reported higher prevalence rates for high risk groups including coinfection with HIV and a history of injecting drug use.

Eligibility for inclusion in the review

The inclusion criteria for this question are summarised briefly below:

- population – pregnant women in the UK
- intervention – N/A
- comparator – N/A
- outcomes – hepatitis C virus; seroprevalence (current and past infection and false positive serology) and current infection prevalence (hepatitis C RNA prevalence)
- study design - cross sectional studies, cohort studies and systematic reviews of these
- date and language - studies published in English after 16th September 2010.

Description of the evidence

Database searches yielded 134 results, of which 25 were judged to be relevant to this question and 5 abstracts met the criteria for full text review. After review of the full texts, 3 studies were included.

Two studies were excluded after review of the full text because they did not report prevalence of hepatitis C for a population of UK pregnant women.

Summary of findings

A study-level summary of data extracted from each included publication is presented in the appraisal of individual studies in Appendix 3. In Appendix 3 publications are stratified by question.

Three UK studies reporting the seroprevalence of hepatitis C in pregnant women were identified (Cortina-Borja et al 2016[13]; Orkin et al 2016[14]; Selvapatt et al 2015[15]). The reported seroprevalence rates varied from 0.095% to 0.5%. Seroprevalence varied according to country of birth, with 1 study reporting a seroprevalence of 0.019% for women born in the UK and a seroprevalence of 0.366% for women born in Eastern Europe[13]. Current infection prevalence was reported by 2 studies and was 0.1%[14] and 0.17%[15] respectively. In the 2 studies that reported the percentage of women who were diagnosed with hepatitis C prior to their pregnancy this was 27%[15] and 40%[14] respectively.

The figures reported in these studies are summarised in Table 3. Further details about the studies are provided in the Appendix 3 tables.

The studies were assessed using the JBI critical appraisal checklist for studies reporting prevalence data. The sample sizes of the studies varied. One study had a small study population[14] and although another was larger, the women were recruited over a long (10-year) period[15]. One study[13] excluded women who did not have a live born infant so women positive for hepatitis C antibodies could have been missed. In 2 studies, only positive samples received confirmation testing, introducing the possibility that false negative tests were missed. In the third study no information was provided on the tests used. Two of the 3 studies were based on women attending clinics in London and the third used a North Thames population of newborn infants born in 2012. The breakdown of results by county of birth or ethnicity shows that prevalence varies for different groups. It is not clear to what extent the prevalence observed in these populations would apply to the UK as a whole.

Table 3. Summary of hepatitis C prevalence in pregnant women in the UK.

	Cortina-Borja et al (2016)[13]	Orkin et al (2106)[14]	Selvapatt et al (2015)[15]
Population	31,467 newborn infants‡ born in the North Thames area in 2012§	1,000 samples from women attending an antenatal clinic at 2 London hospitals** in 2013	35,355 women attending antenatal clinics in 1 London hospital†† from 2003 to 2013
Overall seroprevalence‡‡	0.095% (95%CI 0.067 to 0.136)	0.5% (95%CI 0.06 to 0.94)	0.38% (95%CI not reported)
Overall current infection prevalence§§	---	0.1% (95%CI 0 to 0.3)	0.17% (95%CI not reported)
Seroprevalence by country of birth/ ethnicity	UK: 0.019% Eastern Europe: 0.366% Southern Europe: 0.160% Africa: 0.031% Asia-Pacific: 0.171%	White European: 1.3% Asian: 0.4% African: 0.9% White British and Irish: 0	---
Current infection cases by country of birth/ ethnicity	---	The single current infection case was in a women of African ethnicity	UK: 14 Eastern Europe: 14 Asia: 9 Africa: 4 Western Europe: 3
Seroprevalence by HIV status	0.0032% (95%CI 0.0002 to 0.018)	---	---
Hepatitis C cases by genotype	---	---	Genotype 1: 21 Genotype 2: 4 Genotype 3: 11 Genotype 4: 6 Unknown: 2
Percentage of positive women diagnosed with hepatitis C prior to pregnancy	---	40% (2/5)	27% (16/60)

‡ The presence of hepatitis C antibodies in the newborn infant reflects maternal infection status due to passive transfer of maternal antibodies
§§ Births in the North Thames region accounted for 17% of live births in England and Wales in 2012
** Royal London Hospital and Newham General Hospital
†† St Mary's Hospital
‡‡ Positive test for the presence of antibodies to the hepatitis C virus
§§ Positive test for the presence of the hepatitis C virus

Question 2 – Which risk factors are associated with hepatitis C transmission from mother to child?

The 2011 UK NSC review reported that vertical transmission of hepatitis C from mother to child occurs in 3% to 8% of cases[2] and that viral load is a key risk factor for vertical transmission. The 2011 review also reported that there was no evidence that preventative interventions such as elective Caesarean section might protect against transmission.[2]

Eligibility for inclusion in the review

The inclusion criteria for this question are summarised briefly below:

- population – pregnant women positive for hepatitis C using second, third or fourth generation antibody tests or RNA tests (reported separately)
- exposure – any subgroup, characteristic or clinical or laboratory parameter related to the hepatitis C virus, the mother, the child or the pregnancy and birth process, evaluated for hepatitis C vertical transmission. For example, HIV status, viral load, breastfeeding, premature rupture of membranes etc
- comparator – any subgroup, characteristic or clinical or laboratory parameter related to the hepatitis C virus, the mother, the child or the pregnancy and birth process, used as the reference categories to exposures in the exposure 1 group. For example, HIV status, viral load, breastfeeding, premature rupture of membranes etc
- outcomes – occurrence of hepatitis C as diagnosed by second, third or fourth generation antibody tests or RNA tests in infants, with at least 1 measurement at 15 months or older. Report test results at all assessments and report time/age of each
- study design – case-control studies, cohort studies and systematic reviews of these
- date and language - studies published in English after 16th September 2010.

Description of the evidence

Database searches yielded 134 results, of which 45 abstracts were judged to be relevant to this question and 23 met the criteria for review at full text. After review of the full texts, 6 studies were included.

Reasons for excluding studies after review of the full text were:

- 9 studies with no calculation of the association between risk factors and vertical transmission meeting the inclusion criteria for this question. These included studies where there were no positive cases identified and studies which only tested younger infants (ie no measurement at 15 months or older)
- 4 studies about the mechanism of vertical transmission
- 2 studies focusing on rates of infection and/or transmission
- 1 study focusing on the management of infected infants
- 1 older review superseded by a more recently published review.

Summary of findings

A study-level summary of data extracted from each included publication is presented in the appraisal of individual studies in Appendix 3. In Appendix 3 publications are stratified by question.

Two systematic reviews (Benova et al 2014[7]; Cottrell et al 2013[16]) and 4 individual cohort studies (Ruiz-Extremera et al 2017[17]; Garcia-Tejedor et al 2015[18]; Delotte et al 2014[19]; Ruiz-Extremera et al 2011[20]) assessing risk factors associated with the vertical transmission of hepatitis C were included. An overview of the key risk factors assessed is provided in Table 4, with results from systematic reviews and multivariate analysis prioritised. Factors considered in univariate analysis only are listed in the Appendix 3 tables.

Risk factors with some evidence of an association with vertical transmission included maternal coinfection with HIV; viral load; use of intrapartum procedures (fetal scalp blood sampling and internal electrode); prolonged rupture of membranes, episiotomy and alanine transaminase value in infants. However, the association was not statistically significant in all studies. In addition, children were significantly more likely to test positive for vertical transmission if reporting was based on 1 positive RNA test (compared to 2 positive tests) and if they were assessed at more than 36 months old (compared to children assessed at 18-23 months).

A systematic review (Cottrell et al 2013) found inconsistent evidence about the association between internal fetal monitoring and risk of vertical transmission.

In Cottrell et al's (2013)[16] systematic review some risk factors considered (vaginal birth vs Caesarean; breastfeeding) did not appear to be associated with an increased risk of vertical transmission.
Additional risk factors that were not significantly associated with an increased risk of vertical transmission in multivariate analysis in individual studies included selection of mothers through routine screening (compared to women identified by risk factors) and whether infants were or were not lost to follow-up between birth and testing (Benova et al 2014); presence of HLA-C2C2 ligand in mothers (Ruiz-Extremera et al 2017[17]) and female newborn gender (Garcia-Tejedor et al 2015[18]).

Ruiz-Extremera et al (2017)[17] assessed immunogenetic profile (eg HLA alleles and killer-cell immunoglobulin-like receptors (KIR)) and risk of transmission. A decreased risk of transmission was found in the presence of some immunogenetic factors (eg presence of HLA-C1 ligand in the mother and presence of KIR2DL3 in the child) (see Appendix 3).

The systematic reviews were assessed using the CASP checklist for systematic reviews. There were few concerns with the design of the reviews. Limited details were provided about the populations of the included studies. Samples sizes/ number of data points used in analysis tended to be small. Only one review (Cottrell et al 2013)[16] performed quality assessment of the included studies. Overall, most of the included studies were judged to be of poor quality. Areas of concern included failure to adjust for confounders and small sample sizes.

The individual studies were assessed using the CASP checklist for cohort studies. Study sample sizes were small with women recruited over a long time period, ranging from 4 to 25 years. One study (Garcia-Tejedor et al 2015)[18] used a retrospective design which introduces the possibility of bias through the use of medical records as the data source which may have missing information. One study (Delotte et al (2014)[19] did not perform multivariate analysis. Few studies reported details of any factors adjusted for in their analyses. The reported effect sizes varied and the confidence intervals around the odds ratios reported were generally wide, reducing confidence in the results.

Table 4. Risk factors for vertical transmission.

Risk factor	Population	Key results	Study
Maternal co-infection with HIV (yes/no)	Systematic review (25 data sets) (n not stated)	OR 2.6 95%CI 1.5 to 4.4, p=0.002	Benova et al (2014)[7]
	710 mothers positive for hepatitis C RNA and their 711 children	OR 3.2 95%CI 0.87 to 11.59, p=0.081	Garcia-Tejedor et al (2015)[18]
Prolonged rupture of membranes (vs less prolonged rupture)	Systematic review (2 studies; 245 mother-infant pairs)	No pooled analysis. Significantly associated with increased risk of vertical transmission in both studies (in 1 study for rupture >6 hours: OR 9.3 95%CI 1.5 to 180, p not reported)	Cottrell et al (2013)[16]
Use of intrapartum procedures*** (yes/no)	710 mothers positive for hepatitis C RNA and their 711 children	OR 10.1 95%CI 2.6 to 39.0, p=0.001	Garcia-Tejedor et al (2015)[18]
Episiotomy††† (yes/no)	710 mothers positive for hepatitis C RNA and their 711 children	OR 4.2 95%CI 1.2 to 14.1, p=0.02	Garcia-Tejedor et al (2015)[18]
Detectable hepatitis C viral load (>615 copies/mL vs ≤615 copies/mL)‡‡‡	710 mothers positive for hepatitis C RNA and their 711 children	OR 9.3 95%CI 1.1 to 78.7, p=0.04	Garcia-Tejedor et al (2015)[18]
Hepatitis C viral load (>6 log copies/mL vs ≤6 log copies/mL§§§)	214 mothers positive for hepatitis C antibodies and their 214 children	OR 4 95%CI 1.3 to 12.4, p=0.01****	Delotte et al (2014)[19]
Hepatitis C viral load (>600,000 IU/mL vs ≤600,000 IU/mL)	145 mothers positive for hepatitis C RNA and/or antibodies and their 185 children	OR 7.3 95%CI 1.8 to 29.4, p=0.005	Ruiz-Extremera et al (2011)[20]
ALT value in infant (>40U/L vs ≤40U/L)	145 mothers positive for hepatitis C RNA and/or	OR 5.3 95%CI 1.5 to 18.8, p=0.01	Ruiz-Extremera et al

*** Fetal scalp blood sampling and internal electrode
††† Episiotomy is a surgical cut made at the opening of the vagina during childbirth
‡‡‡ The detectable viral load threshold was chosen based on the most sensitive detection available during the earliest years of the study
§§§ 6 log copies/ml is equivalent to 1,000,000IU/ml
**** This study only performed univariate analysis

	antibodies and their 185 children		(2011)[20]
Internal fetal monitoring (yes/no)	Systematic review (3 studies; 928 mother-infant pairs)	No pooled analysis. Conflicting results from the 3 studies, with 1 study showing an increased risk of transmission and 2 studies showing no increased risk	Cottrell et al (2013)[16]
Breastfeeding (yes/no)	Systematic review (14 studies; 2,971 mother-infant pairs)	No pooled analysis. No study found a significant association between risk of transmission and breastfeeding	Cottrell et al (2013)[16]
Vaginal delivery (vs any Caesarean)	Systematic review (11 studies; 2,308 mother-infant pairs)	No pooled analysis. 10 of 11 studies found no statistically significant difference in risk of transmission for Caesarean vs vaginal birth	Cottrell et al (2013)[16]
Vaginal delivery or emergency Caesarean (vs elective Caesarean)	Systematic review (4 studies; 2,080 mother-infant pairs)	No pooled analysis. 2 good quality studies found no statistically significant association. 2 fair quality studies had conflicting results	Cottrell et al (2013)[16]
Selection of mothers through routine screening (vs women identified by risk factors)	Systematic review (25 data sets) (n not stated)	OR 1.82 95%CI 0.95 to 3.48, p=0.07	Benova et al (2014)[7]
Loss to follow-up between birth and hepatitis C status determination (yes/no)	Systematic review (25 data sets) (n not stated)	OR 1.88 95%CI 0.91 to 3.85, p=0.08	Benova et al (2014)[7]
Presence of HLA-C2C2 ligand in mothers (yes/no)	79 mothers positive for hepatitis C RNA and their 98 children	OR 1.80 95%CI 0.32 to 1.05, p=0.501	Ruiz-Extremera et al (2017)[17]
Newborn gender female (vs male)	710 mothers positive for hepatitis C RNA and their 711 children	OR 2.62 95%CI 0.91 to 7.55, p=0.075	Garcia-Tejedor et al (2015)[18]

ALT - alanine transaminase; CI – confidence intervals; OR – odds ratio

Summary of Findings Relevant to Criteria 1: Criteria not met

Two questions were considered for this criterion, relating to the seroprevalence and current infection prevalence of hepatitis C in pregnant women in the UK and the risk factors associated with hepatitis C transmission from mother to child.

This 2011 UK NSC evidence review reported an overall prevalence for hepatitis C virus of between 0.29% and 0.40% from UK studies, but also reported higher prevalence rates for high risk groups. The current review identified 3 new UK studies from the South East of England with varied sample sizes. The reported seroprevalence rates were between 0.095% to 0.5% and seroprevalence varied according to country of birth. Current infection prevalence (from 2 London populations) was between 0.1% and 0.17%. It is not clear to what extent the prevalence observed in these populations would apply to the UK as a whole. It is also not clear how many cases detected in pregnancy would be new, previously undiagnosed cases of hepatitis C.

The 2011 UK NSC review reported that transmission of hepatitis C from mother to child occurs in 3% to 8% of cases and that viral load is a key risk factor for vertical transmission. The current review also identified high viral load as a risk factor for increased vertical transmission. Maternal co-infection with HIV was also identified as increasing the risk of vertical transmission. Several factors relating to the birth process were found to be associated with an increased risk of vertical transmission, including the use of intrapartum procedures, prolonged rupture of membranes, episiotomy and possibly internal fetal monitoring, although there were conflicting results for this. One small study also showed an association between alanine transaminase levels in the infant and an increased risk of vertical transmission. In a systematic review vaginal birth compared to Caesarean section and breastfeeding were not associated with an increased risk of vertical transmission. The study sample sizes were generally small. The reported effect sizes varied and confidence intervals around the odds ratios were generally wide reducing confidence in the result.

UK studies on the seroprevalence and current infection prevalence of hepatitis C in pregnant women were identified. However, it is not clear how generalisable these results would be to the UK as a whole. It is also

uncertain how many new cases would be detected during pregnancy. Risk factors significantly associated with an increased risk of vertical transmission were identified. However, many of the studies were of low quality and the evidence for some risk factors was inconsistent. Given the uncertainties in the evidence base, criterion 1 is not met.

Criterion 4 – There should be a simple, safe, precise and validated screening test

Question 3 – What is the diagnostic accuracy of second, third and fourth generation antibody tests for the detection of hepatitis C?

The 2003 UK NSC review[4] cited a sensitivity of 98.9% and specificity of 100% for third generation tests for hepatitis C in adults with chronic liver disease. The 2003 review also reported a specificity of between 96% and 99% for blood donors. The 2003 review stated that there were few studies assessing test performance in general populations or pregnant women, but did cite one small study of pregnant women in Taiwan. This reported a sensitivity and specificity of 100% and 66% for a third generation assay. The 2003 review argued that due to the low prevalence of hepatitis C in the UK, low positive predictive values, and therefore a high number of false positive tests, would be expected.

Eligibility for inclusion in the review

The inclusion criteria for this question are summarised briefly below:

- population – pregnant women or general population if insufficient studies in the population of interest
- index tests – any second to fourth generation test to detect antibodies for hepatitis C using serological methods, including ELISA, EIA, CLIA or immunoblots
- reference standard – any test used to detect hepatitis C RNA, for example, polymerase chain reaction or NAAT
- outcomes – sensitivity, specificity; positive predictive value (PPV); negative predictive value (NPV)
- study design - cross-sectional studies, cohort studies and systematic reviews of these. Studies in randomly assigned or consecutively enrolled populations should be prioritised
- date and language - studies published in English after 2003.

Description of the evidence

Database searches yielded 134 results, of which 33 were judged to be relevant to this question and 10 abstracts met the criteria for review at full text. After review of the full texts, no studies were included in the review.

Reasons for excluding studies after review of the full text were:

- 3 studies looking at the performance of screening strategies (eg risk groups to test)
- 2 studies using laboratory samples to assess new tests
- 1 study that did not test performance in a population of pregnant women or a general population
- 1 study that did not report details of the study population. The sample had a prevalence of 20% compared to a reported general population prevalence of 1% for this country
- 1 study assessing the ability of a test to detect low concentrations of antibodies
- 1 study assessing the performance of a risk based screening questionnaire
- 1 case control study.

Summary of findings

No studies published after 2003 that assessed the diagnostic accuracy of antibody tests for the detection of hepatitis C in pregnant women or a general population were identified. The test related studies that were identified tended to assess the performance of new tests in a laboratory setting using a combination of stored samples from individuals known to be at high or low risk of hepatitis C.

The prevalence of hepatitis C antibodies in the population tested will influence the test performance scores, particularly affecting positive predictive value (PPV). Lower positive predictive scores are associated with a higher proportion of false positive tests. In Table 5 the test performance scores for a population of pregnant women reported from the 2003 UK NSC review (ie sensitivity 100%, specificity 66%) have been applied to the latest estimates for the UK seroprevalence of hepatitis C in pregnant women discussed in question 1.

Table 5. Test performance by seroprevalence.

Seroprevalence of hepatitis C	Sensitivity	Specificity	PPV	NPV
0.095%	100%	66%	0.3%	100%
0.5%	100%	66%	1.5%	100%
0.38%	100%	66%	1.1%	100%

NPV – negative predictive value; PPV - positive predictive value

As demonstrated in Table 5, in populations with a low seroprevalence for hepatitis C antibodies screening would generate a high proportion of false positive screening tests. False positive tests can cause anxiety and lead to women undergoing additional unnecessary tests. Negative predictive values remained high for all of the seroprevalence values modelled suggesting that a low number of false negatives would be expected, reducing the chance that women with hepatitis C would be missed.

Summary of Findings Relevant to Criteria 4: Criteria not met

The 2003 UK NSC review cited one small study of pregnant women in Taiwan reporting a sensitivity and specificity of 100% and 66% for a third generation assay.

The current review did not identify any new studies assessing the diagnostic accuracy of antibody tests for the detection of hepatitis C in pregnant women or a general population to add to the findings of the 2003 review.

Applying the test performance scores in pregnant women from the 2003 review to the latest estimates for the UK seroprevalence of hepatitis C in pregnant women resulted in very low positive predicative values. This suggests that screening all UK pregnant women for hepatitis C may result in a high number of false positive tests.

As the evidence on screening test performance for hepatitis C in pregnant women comes from 1 small study and screening for hepatitis C in the UK is likely to generate a high number of false positive tests criterion 4 is not met.

Criterion 9 –There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is not prospect of benefit to the individual screened then the screening programme shouldn't be further considered.

Question 4 – What is the reported effectiveness of direct acting antivirals (DAAs) in pregnancy for the prevention of hepatitis C vertical transmission and hepatitis C associated morbidity in pregnant women?

This question has not previously been considered in a UK NSC evidence review.

Eligibility for inclusion in the review

The inclusion criteria for this question are summarised briefly below:

- population – pregnant women
- intervention – direct acting antivirals
- comparator – any or none
- outcomes – primary outcome: percentage of hepatitis C transmission from mother to infant. Secondary outcomes: any hepatitis C related pregnancy or childbirth outcome investigated eg hypertension, antepartum haemorrhage and cholestasis of pregnancy; cure rates; adverse events from treatment
- study design – in order of preference: RCTs, quasi-experimental studies; cohort studies, case-controlled studies and systematic reviews of these.
- date and language - studies published in English after 16th September 2010.

If no studies on pregnant women are identified, studies on the effectiveness of DAAs in a general population of adults with hepatitis C on hepatitis C related morbidity can be presented as a narrative summary for context.

Description of the evidence

Database searches yielded 134 results, of which 20 abstracts were judged to be relevant to this question and 5 met the criteria for review at full text. After review of the full texts no studies were included in the review.

Reasons for excluding studies after review of the full text were:

- 3 descriptive reviews/ commentary
- 2 reviews of DAA use in adults generally (ie not on use in pregnant women).

Summary of findings

No studies were identified assessing the effectiveness of direct acting antivirals (DAAs) in pregnancy.

Evidence on the use of DAAs in a general population from a recent systematic review (Jakobsen et al 2017[11]) is briefly summarised along with current NICE guidance on the use of DAAs. The systematic review is not included in the Appendix 3 tables and has not been formally appraised.

Between February 2015 and February 2018, NICE issued 8 technology appraisals recommending various DAAs for the treatment of hepatitis C. Specific recommendations vary for different hepatitis C virus genotypes and according to whether the person has cirrhosis or previous treatment history. All of these recommendations relate to adults with hepatitis C.

A recent Cochrane review (Jakobsen et al 2017[11]) assessed the benefits and harms of DAAs in people with chronic hepatitis C. This review included 138 randomised controlled trials published up to October 2016, covering 51 different DAAs, including some which have been withdrawn. The trials were generally short-term trials with an average intervention period of 14 weeks and an average follow-up period of 34 weeks. They mainly assessed sustained virologic response. The review authors judged the quality of the evidence to be low or very low quality with all of the included trials at high risk of bias. Overall, the review authors:

- confirmed previous findings that DAAs reduce the number of people who have detectable hepatitis C virus in their blood compared to controls
- found insufficient data to address their primary outcome on the impact of DAAs that are currently on the market or in development on hepatitis C related morbidity or all-cause mortality
- found that 1 DAA (simeprevir) showed evidence of a lower risk of a serious adverse events compared to placebo.

A discussion paper (Bernstein et al 2018[21]), referenced a phase 1 trial in progress on the use of DAAs in pregnant women with an expected completion date of 2019 (NCT02683005).

Question 5 – What is the reported effectiveness of DAAs in children with vertically acquired hepatitis C on hepatitis C associated morbidity and cure?

This question has not previously been considered in a UK NSC evidence review.

Eligibility for inclusion in the review

The inclusion criteria for this question are summarised briefly below:

- population – children with vertically transmitted hepatitis C or if not available, children with hepatitis C treated before the age of 5
- intervention – direct acting antivirals
- comparator – treatment of children after onset of hepatitis C symptoms, or, if not available, any or none
- outcomes – any hepatitis C related outcome investigated eg cure rates, liver damage, ALT levels, cirrhosis, obesity, adverse events from treatment
- study design – in order of preference: RCTs, quasi-experimental studies; cohort studies, case-controlled studies and systematic reviews of these
- date and language - studies published in English after 16th September 2010.

If no studies on the population of interest are identified, studies on the effectiveness of DAAs in a general population of children with hepatitis C

on hepatitis C morbidity can be presented as a narrative summary for context.

Description of the evidence

Database searches yielded 134 results, of which 11 abstracts were judged to be relevant to this question and 5 met the criteria for review at full text. After review of the full texts, no studies were included in the review.

Reasons for excluding studies after review of the full text were:

- 2 studies where the treatment was not a DAA
- 1 review on all treatments for hepatitis C in children of all ages (no information on how infection was acquired)
- 1 study including a population of children aged 5 to 18, primarily infected through non-vertical transmission routes
- 1 study with a mixed population and interventions focusing on the concordance of results at different follow-up periods.

Summary of findings

No studies were identified assessing the effectiveness of direct acting antivirals (DAAs) in children with vertically acquired hepatitis C or children with hepatitis C treated before the age of 5.

Evidence on the use of DAAs in a general population of children from a recent systematic review (Indolfi et al 2017[5]) and an individual study (Hashmi & Cheema 2017[22]) is briefly summarised. These studies are not included in the Appendix 3 tables and have not been formally appraised.

Indolfi et al (2017[5]) produced a review and position paper on behalf of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition. This stated that in 2017, the European Medicines Agency approved the use of ledipasvir/sofosbuvir and sofosbuvir/ribavirin for the treatment of adolescents aged 12 to 17 years weighing more than 35kg for various hepatitis C virus genotypes. Indolfi et al included 2 studies published in full and 3 conference abstracts on the effectiveness of DAAs in children. All the studies were uncontrolled studies in which all patients received a DAA. In the meta-analysis of these studies, the sustained viralologic response (SVR) with DAA was 98.1% (95%CI 96.2 to 99.3).

Hashmi & Cheema (2017) examined the effectiveness of a combination of sofosbuvir and ribavirin in 35 children aged 5 to 18 years (mean age 10.24 ± 2.80 years). Most of the children had a pre-existing haematological disorder and 15 (43%) had acquired hepatitis C through blood product transfusion. Perinatal transmission was documented for 7 children. Outcomes were assessed at 12 weeks after the completion of treatment. The authors reported that an SVR was achieved by 34 of the 35 children with no serious side effects.

Indolfi et al referenced a number of studies on direct acting antivirals in children and adolescents in progress, with expected completion dates between 2018 and 2022.[5]

Summary of Findings Relevant to Criterion 9: Criterion not met

Two questions were considered for this criterion. The first question related to the effectiveness of DAAs in pregnancy for the treatment of the mother and prevention of vertical transmission to the infant. The second question related to the effectiveness of DAAs in children with vertically acquired DAAs.

These questions have not been previously reviewed by the UK NSC.

No studies were identified on the effectiveness of DAAs in pregnancy. Studies have reported high levels of sustained virologic response with DAAs in general populations of adults and children. However, no studies specifically examining the effectiveness of DAAs in children with vertically acquired hepatitis C or younger children were identified.

Studies on the safety and effectiveness of direct acting antivirals in pregnant women and children and adolescents are in progress with expected completion dates between 2018 and 2022.

In the absence of evidence for the effectiveness of DAAs in the populations of interest, this criterion is not met.

Review summary

Conclusions and implications for policy

This report is an update review on systematic antenatal screening for hepatitis C against select UK NSC criteria for appraising the viability, effectiveness and appropriateness of a screening programme. This review assessed key questions to determine if new evidence published since September 2010 suggests that reconsideration of the current recommendation for screening for hepatitis C in the UK is required.

The volume, quality and direction of new evidence published since September 2010 does not indicate that there have been any significant changes in the evidence base since the previous review. Areas of uncertainty relate to:

- the seroprevalence and current infection prevalence for pregnant women for the UK as a whole is unclear, as is the number of new hepatitis C cases that would be detected by screening pregnant women
- there are uncertainties about which risk factors increase the risk of vertical transmission and to what extent
- there is limited information about the performance of screening tests in pregnant women. The limited evidence available suggests a high proportion of false positives would result from screening
- there is an absence of evidence about the effectiveness of treatment with DAAs for pregnant women and children with vertically acquired hepatitis C.

The current recommendation not to introduce a UK systematic antenatal population screening programme for hepatitis C should be retained.

The evidence relating to the effectiveness of treatment with DAAs for pregnant women and children with vertically acquired hepatitis C should be kept under review.

Limitations

A limitation for this review is the lack of evidence specific to the population of interest for population-based screening for hepatitis C, particularly relating to the performance of screening tests in pregnant women or the effectiveness of treatment in pregnant women or children with vertically acquired hepatitis C.

This rapid review process was conducted over a condensed period of time (approximately 12 weeks). Searching was limited to 3 bibliographic databases and did not include grey literature sources. The review was guided by a protocol developed a priori. The literature search and first appraisal of search results were undertaken by 1 information scientist, and further appraisal and study selection by 1 reviewer. Any queries at both stages were resolved through discussion with a second reviewer. Studies not available in the English language, abstracts and poster presentations, were not included. Studies that were not published in peer-reviewed journals were not reviewed.

Appendix 1 — Search strategy

Electronic databases

The search strategy included searches of the databases shown in Table 6.

Table 6. Summary of electronic database searches and dates.

Database	Platform	Searched on date	Date range of search
MEDLINE	Ovid SP	21st February 2018	2010 to Present (Q1,2,4,5) 2003 to Present (Q3)
Embase	Ovid SP	21st February 2018	2010 to Present (Q1,2,4,5) 2003 to Present (Q3)
The Cochrane Library	Wiley Online	21st February 2018	2010 to Present (Q1,2,4,5) 2003 to Present (Q3)

Search Terms

Search terms for MEDLINE are shown in Table 7. A similar search was conducted for Embase. Search terms for the Cochrane Library databases are shown in Table 8.

Table 7. Search strategy for MEDLINE.

#	Search terms	Results
Question 1		
1	exp Hepatitis C/	57231
2	hep$ c.tw.	68599
3	hcv.tw.	51090
4	1 or 2 or 3	86515
5	Pregnant Women/	6510
6	exp Pregnancy/	826777
7	preconception care/ or prenatal care/	25261
8	Maternal Health/	606
9	(pregnan* or antenat* or ante-nat* or antepart* or ante-part* or prenat* or pre-nat* or prepart* or pre-part* or maternal or mother*).ti,ab.	723551
10	5 or 6 or 7 or 8 or 9	1106275
11	4 and 10	1957
12	((pregnan* or antenat* or ante-nat* or antepart* or ante-part* or prenat* or pre-nat* or prepart* or pre-part* or maternal or mother*) adj5 (hep$ c or hcv*)).tw.	715
13	11 or 12	1957
14	prevalence/	247010
15	Cross-Sectional Studies/	257115

16	(prevalence or seroprevalence or sero-prevalence).ti,ab. or epidemiolog*.ti.	616373
17	(crosssectional or cross-sectional).ti,ab.	269405
18	14 or 15 or 16 or 17	965561
19	13 and 18	652
20	exp United Kingdom/	341134
21	(united kingdom or uk or britain or british or gb or england or northern ireland or scotland or wales or nhs).ti,ab,in.	1461643
22	20 or 21	1642177
23	19 and 22	69
24	limit 23 to (english language and yr="2010 -Current")	29
Question 2		
1	exp Hepatitis C/	57231
2	hep$ c.tw.	68599
3	hcv.tw.	51090
4	1 or 2 or 3	86515
5	Pregnant Women/	6510
6	exp Pregnancy/	826777
7	preconception care/ or prenatal care/	25261
8	Maternal Health/	606
9	(pregnan* or antenat* or ante-nat* or antepart* or ante-part* or prenat* or pre-nat* or prepart* or pre-part* or maternal or mother*).ti,ab.	723551
10	5 or 6 or 7 or 8 or 9	1106275
11	4 and 10	1957
12	((pregnan* or antenat* or ante-nat* or antepart* or ante-part* or prenat* or pre-nat* or prepart* or pre-part* or maternal or mother*) adj5 (hep$ c or hcv*)).tw.	715
13	11 or 12	1957
14	infectious disease transmission, vertical/	14093
15	(vertical adj5 transmi*).ti,ab.	6252
16	exp Delivery, Obstetric/ and disease transmission, infectious/	5
17	((mother* or maternal) adj2 (neonat* or infant* or child* or f?etal or f?etus*) adj5 transmi*).ti,ab.	6773
18	14 or 15 or 16 or 17	20321
19	4 and 18	917
20	exp Hepatitis C/tm	5616
21	transmi*.ti.	84527
22	20 or 21	88685
23	13 and 22	743
24	19 or 23	1140
25	limit 24 to (english language and yr="2010 -Current")	237
26	(case reports or comment or editorial or letter or news or "review").pt.	5647694
27	25 not 26	150
28	limit 25 to "reviews (maximizes specificity)"	12
29	27 or 28	158
Question 3		
1	exp Hepatitis C/	57231
2	hep$ c.tw.	68599
3	hcv.tw.	51090
4	1 or 2 or 3	86515
5	Pregnant Women/	6510
6	exp Pregnancy/	826777
7	preconception care/ or prenatal care/	25261

8	Maternal Health/	606
9	(pregnan* or antenat* or ante-nat* or antepart* or ante-part* or prenat* or pre-nat* or prepart* or pre-part* or maternal or mother*).ti,ab.	723551
10	5 or 6 or 7 or 8 or 9	1106275
11	4 and 10	1957
12	((pregnan* or antenat* or ante-nat* or antepart* or ante-part* or prenat* or pre-nat* or prepart* or pre-part* or maternal or mother*) adj5 (hep$ c or hcv*)).tw.	715
13	11 or 12	1957
14	diagnostic tests, routine/	9737
15	Mass screening/	92718
16	Serologic Tests/	18837
17	exp Enzyme-Linked Immunosorbent Assay/	140954
18	Polymerase Chain Reaction/	232777
19	(screen* or test or tests or testing or detect*).tw.	4066595
20	(enzyme linked immunosorbent assay* or elisa or enzyme immunoassay* or eia or recombinant immunoblot assay* or riba).tw.	207999
21	(polymerase chain reaction or pcr).tw.	542208
22	serologic.tw.	25352
23	((sero* adj5 diagnos*) or (serotest* or seroscreen* or serodiagnos*)).tw.	19205
24	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	4575997
25	13 and 24	1024
26	prenatal diagnosis/ or maternal serum screening tests/	34734
27	4 and 26	44
28	25 or 27	1027
29	exp "Sensitivity and Specificity"/	516707
30	(sensitiv* or specific* or sn or sp or predict* or ppv or npv or likelihood ratio* or nlr or plr or accura*).tw.	5034040
31	False Positive Reactions/ or False Negative Reactions/	36804
32	(false positive* or false negative*).tw.	68058
33	29 or 30 or 31 or 32	5238373
34	28 and 33	226
35	limit 34 to (english language and yr="2003 -Current")	114
36	(case reports or comment or editorial or letter or news or "review").pt.	5647694
37	35 not 36	86
38	limit 28 to "reviews (maximizes specificity)"	25
39	limit 38 to (english language and yr="2003 -Current")	20
40	37 or 39	102
Question 4		
1	exp Hepatitis C/	57231
2	hep$ c.tw.	68599
3	hcv.tw.	51090
4	1 or 2 or 3	86515
5	Pregnant Women/	6510
6	exp Pregnancy/	826777
7	preconception care/ or prenatal care/	25261
8	Maternal Health/	606
9	(pregnan* or antenat* or ante-nat* or antepart* or ante-part* or prenat* or pre-nat* or prepart* or pre-part* or maternal or mother*).ti,ab.	723551
10	5 or 6 or 7 or 8 or 9	1106275

11	4 and 10	1957
12	((pregnan* or antenat* or ante-nat* or antepart* or ante-part* or prenat* or pre-nat* or prepart* or pre-part* or maternal or mother*) adj5 (hep$ c or hcv*)).tw.	715
13	11 or 12	1957
14	Antiviral Agents/	69479
15	(((antiviral or anti-viral) adj5 (therap* or treatment* or agent*)) or antivirals or anti-virals).tw.	30760
16	(glecaprevir or grazoprevir or paritaprevir or simeprevir or voxilaprevir or daclatasvir or elbasvir or ledipasvir or ombitasvir or pibrentasvir or velpatasvir or sofosbuvir or dasabuvir).tw.	2363
17	polymerase inhibitor?.tw.	1915
18	((ns3* or ns5*) adj2 inhibitor?).tw.	1438
19	treatment outcome/	825772
20	drug therapy/	29454
21	14 or 15 or 16 or 17 or 18 or 19 or 20	931482
22	13 and 21	257
23	limit 22 to (english language and yr="2010 -Current")	113
24	(case reports or comment or editorial or letter or news or "review").pt.	5647694
25	23 not 24	63
26	limit 23 to "reviews (maximizes specificity)"	7
27	25 or 26	70
Question 5		
1	exp Hepatitis C/	57231
2	hep$ c.tw.	68599
3	hcv.tw.	51090
4	1 or 2 or 3	86515
5	exp child/ or exp infant/	2276111
6	(child* or schoolchild* or preschooler* or pre-schooler* or girl* or boy* or infant* or baby or babies).tw.	1626803
7	5 or 6	2742898
8	4 and 7	6592
9	((child* or schoolchild* or preschooler* or pre-schooler* or girl* or boy* or infant* or baby or babies) adj5 (hep$ c or hcv*)).tw.	1328
10	8 or 9	6600
11	Antiviral Agents/	69479
12	(((antiviral or anti-viral) adj5 (therap* or treatment* or agent*)) or antivirals or anti-virals).tw.	30760
13	(glecaprevir or grazoprevir or paritaprevir or simeprevir or voxilaprevir or daclatasvir or elbasvir or ledipasvir or ombitasvir or pibrentasvir or velpatasvir or sofosbuvir or dasabuvir).tw.	2363
14	polymerase inhibitor?.tw.	1915
15	((ns3* or ns5*) adj2 inhibitor?).tw.	1438
16	treatment outcome/	825772
17	drug therapy/	29454
18	11 or 12 or 13 or 14 or 15 or 16 or 17	931482
19	10 and 18	1258
20	limit 19 to (english language and yr="2010 -Current")	576
21	(case reports or comment or editorial or letter or news or "review").pt.	5647694
22	20 not 21	445
23	limit 20 to "reviews (maximizes specificity)"	15
24	22 or 23	456

Table 8. Search strategy for the Cochrane Library Databases.

#	Search terms
#1	MeSH descriptor: [Hepatitis C] explode all trees
#2	hepatitis c or "hep c" or hcv:ti,ab,kw (Word variations have been searched)
#3	#1 or #2
#4	pregnan* or antenat* or ante-nat* or antepart* or ante-part* or prenat* or pre-nat* or prepart* or pre-part* or maternal or mother*:ti,ab,kw (Word variations have been searched)
#5	child* or schoolchild* or preschooler* or pre-schooler* or girl* or boy* or infant* or baby or babies
#6	#4 or #5
#7	#3 and #6

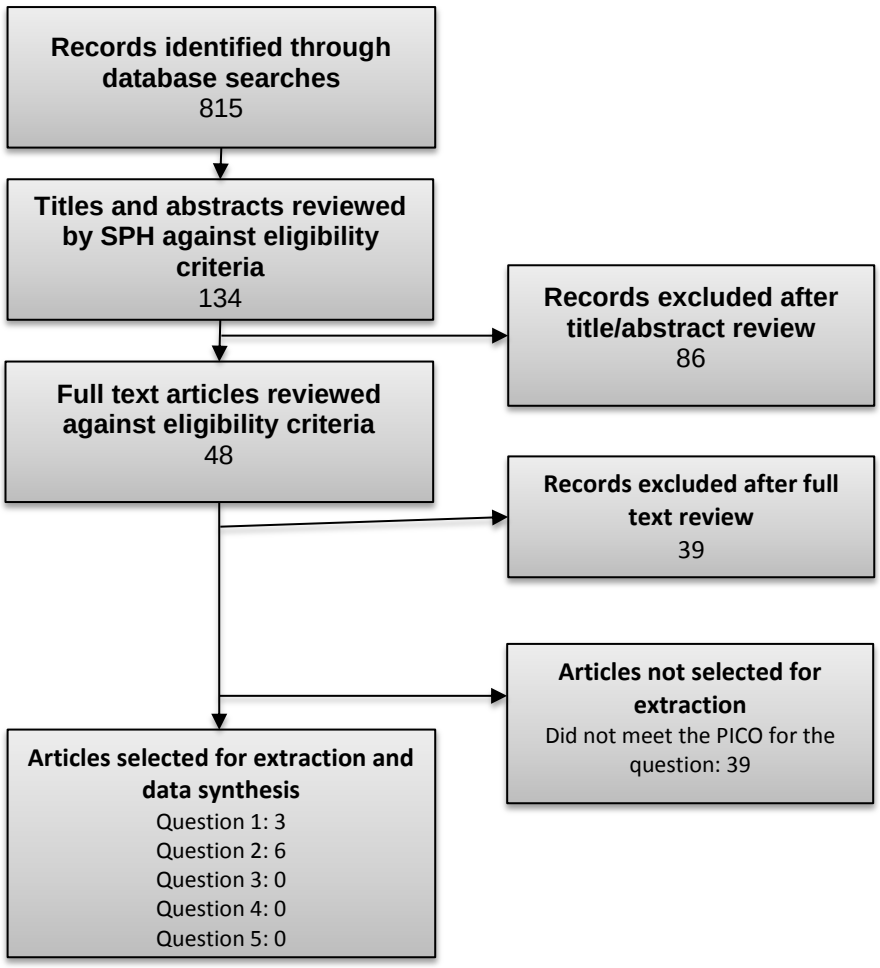
Duplicate references were removed.

Appendix 2 — Included and excluded studies

PRISMA flowchart

Figure 2 summarises the volume of publications included and excluded at each stage of the review. Forty-eight publications were ultimately judged to be relevant to 1 or more review questions and were considered for extraction. Publications that were included or excluded after the review of full text articles are detailed below.

Figure 2. Summary of publications included and excluded at each stage of the review.



Publications included after review of full text articles

The 9 publications included after review of full texts are summarised in Table 9. Studies meeting the PICO inclusion/ exclusion criteria for each individual question were included. No new studies meeting the inclusion criteria were identified for the test or intervention criteria.

Table 9. Summary of publications included after review of full text articles, and the criteria each publication was identified as being relevant to.

Study	The condition	The test	The intervention	Comments
Cortina-Borja et al (2016)	x			
Orkin et al (2016)	x			
Selvapatt et al (2015)	x			
Benova et al (2014)	x			
Cottrell et al (2013)	x			
Ruiz-Extremera et al (2017)	x			
Garcia-Tejedor et al (2015)	x			
Delotte et al (2014)	x			
Ruiz-Extremera et al (2011)	x			

Appendix 3 — Summary and appraisal of individual studies

Data extraction and quality assessment for studies relevant to criteria 1

Key question 1: What is the seroprevalence and current infection prevalence of hepatitis C virus in pregnant women in the UK?

Table 10. Cortina-Borja et al (2016)[13]

Publication	Cortina-Borja M. Williams D. Peckham CS. Bailey H. Thorne C. Hepatitis C virus seroprevalence in pregnant women delivering live-born infants in North Thames, England in 2012. Epidemiol. Infect. 2016, 144: 627-634
Study details	Cohort study assessing the prevalence of hepatitis C in pregnant women
Study objectives	To assess the prevalence of hepatitis C in pregnant women through testing newborn infants†††† born in the North Thames area in 2012
Inclusions	None stated
Exclusions	None stated
Population	31,467 residual neonatal dried blood spot samples collected as part of routine metabolic newborn screening
Intervention	N/A
Comparator	N/A
Outcomes	Particle agglutination was used to test for hepatitis C. All positive results were repeated and tested with unsensitised particles to rule out non-specific reactions 30 samples tested positive for hepatitis C antibodies, equating to a seroprevalence of 0.095% (95%CI 0.067 to 0.136). The country of birth (and seroprevalence) for the 30 positive samples was: • UK: 3 (0.019%) • Eastern Europe: 11 (0.366%) • Southern Europe: 1 (0.160%) • Africa: 1 (0.031%) • Asia-Pacific: 10 (0.171%) • Unknown: 4 1 woman had coinfection with HIV, equating to a prevalence of hepatitis C/ HIV co-infection of 0.0032% (95%CI 0.0002 to 0.018) Seroprevalence was higher in metropolitan areas (inner and outer London) (0.116%) than non-metropolitan areas (0.053%). This difference was not statistically significant No information was provided on genotype or the number of women that were previously known to have hepatitis C

†††† The presence of hepatitis C antibodies in the newborn infant reflects maternal infection status due to passive transfer of maternal antibodies

Quality appraisal	The study was assessed using the JBI critical appraisal checklist for studies reporting prevalence data. The sample size was large (representing 17% of live births in England and Wales) and from babies born in a geographical area during 1 year. The study used newborn samples to assess seroprevalence in mothers. This approach excluded women who did not have a live born infant. The percentage of women who refused to participate in the newborn screening was low (<0.01%). Only positive test samples received confirmation testing.

Table 11. Orkin et al (2016)[14]

Publication	Orkin C. Jeffery-Smith A. Foster GR. Tong CYW. Retrospective hepatitis C seroprevalence screening in the antenatal setting – should we be screening antenatal women? BMJ Open 2016, 6: e010661
Study details	Retrospective cohort study assessing the prevalence of hepatitis C in pregnant women
Study objectives	To assess the prevalence of hepatitis C in pregnant women who attended 2 London hospitals (Royal London Hospital and Newham General Hospital)
Inclusions	Samples including details of age, ethnicity and postcode
Exclusions	None stated
Population	1,000 sequential stored samples taken from women aged over 18 years who had attended an antenatal clinic at 2 London hospitals during 2013. 48% of the population were Asian, 15% white European, 12% white British and Irish and 11% African
Intervention	N/A
Comparator	N/A
Outcomes	Samples were tested for hepatitis C antibodies using EIA assay and reactive samples were tested for HCV RNA 5 women tested positive for hepatitis C antibodies, equating to a seroprevalence of 0.5% (95%CI 0.06 to 0.94). 2 of the 5 positive samples had a previous positive test recorded on the hospital system • 2 of the positive tests were from women of white European ethnicity (a seroprevalence of 1.3%‡‡‡‡) • 2 from women of Asian ethnicity (a seroprevalence of 0.4%‡‡‡‡) • 1 from a woman of African ethnicity (a seroprevalence of 0.9%‡‡‡‡) 1 of the 5 samples (20%) tested positive for hepatitis C RNA, equating to a current infection prevalence of 0.1% (95%CI 0 to 0.3). The woman with a positive sample had a previous positive test recorded on the hospital system. The ethnicity of this woman was African There were no cases of co-infection with HIV or hepatitis B No information was provided on genotype
Quality appraisal	The study was assessed using the JBI critical appraisal checklist for studies reporting prevalence data. The sample size was small and from a retrospective database. Confirmation testing was only performed on positive screening samples.

‡‡‡‡ Calculated by the review authors

Table 12. Selvapatt et al (2015)[15]

Publication	Selvapatt N. Ward T. Bailey H. et al. Is antenatal screening for hepatitis C virus cost-effective? A decade's experience at a London centre. Journal of Hepatology 2015, 63: 797-804
Study details	Study on the cost-effectiveness of screening, containing data on the prevalence of hepatitis C in pregnant women
Study objectives	To assess the prevalence of hepatitis C in pregnant women attending 1 London hospital (St Mary's Hospital)
Inclusions	None stated
Exclusions	None stated
Population	35,355 pregnant women attending 'booking in visits' at antenatal clinics in 1 London hospital between November 2003 and March 2013
Intervention	N/A
Comparator	N/A
Outcomes	Only data on the prevalence of hepatitis C has been extracted from this study 136 women tested positive for hepatitis C antibodies, equating to a seroprevalence of 0.38% 60 of the 136 women (44%) were positive for hepatitis C RNA, equating to a current infection prevalence of 0.17%. Of these 44 (73%) were new diagnoses and 16 (27%) had a prior diagnosis of hepatitis C For the 44 women with a new diagnosis of hepatitis C: • No women were co-infected with HIV or hepatitis B • 14 (32%) were born in the UK, 14 (32%) in Eastern Europe, 9 (20%) in Asia, 4 (9%) in Africa and 3 (7%) in Western Europe • 21 (48%) were genotype 1, 4 (9%) genotype 2, 11 (25%) genotype 3 and 6 (14%) genotype 4. The genotype of 2 women was unknown • 11 (25%) had a prior history of injecting drug use
Quality appraisal	The study was assessed using the JBI critical appraisal checklist for studies reporting prevalence data. The sample size was moderate with data from 1 centre over a 10 year period. Demographic data was only provided for the new cases of hepatitis C identified. No details were provided about the tests used to detect hepatitis C antibodies or RNA. No details were provided on the response rate ie the number of women offered the test who consented

Key question 2: Which risk factors are associated with hepatitis C transmission from mother to child?

Systematic reviews

Table 13. Benova et al (2014)[7]

Publication	Benova L. Mohamoud YA. Calvert C. Abu-Raddad LJ. Vertical transmission of hepatitis C virus: systematic review and meta-analysis. Clinical Infectious Diseases 2014, 59(6): 765-773
Study details	Systematic review and meta-analysis
Study objectives	To update current estimates of hepatitis C vertical transmission according to maternal HIV coinfection and to determine vertical transmission risk
Inclusions	Studies published up to May 2013 that: • analysed primary data to estimate risk of vertical transmission • specified the age at which infection status was determined • used second-generation or later tests to detect hepatitis C antibodies Risk estimates of vertical transmission were included where the HIV status was known and reported separately and where >11 children were assessed for infection at follow-up and where children were followed up for ≥18 months
Exclusions	Studies that did not provide any details about the antibody test used if they were using data collected prior to 1993, or studies published after 2003 if no data on antibody test or year of data collection were provided
Population	109 studies and 70 data points met the criteria for inclusion. Number of women in the included studies ranged from 23 to 897
Intervention	N/A
Comparator	N/A
Outcomes	Meta-analysis of the risk of vertical transmission from antibody positive and RNA positive women • HIV negative women (n=2,017): 5.8% (95% CI 4.2 to 7.8; I^2 45.9%, p=0.02) • HIV positive women (n=495): 10.8% (95%CI 7.6 to 15.2; I^2 28.8%, p=0.19) In multivariable analysis (25 data sets, number of participants not stated) higher odds of vertical transmission were significantly associated with maternal co-infection with HIV (odds ratio (OR) 2.56 95%CI 1.50 to 4.43, p=0.002) In multivariable analysis children were also more significantly likely to test positive for vertical transmission for: • reporting 1 positive RNA test compared to ≥2 positive RNA tests (OR 2.10 95%CI 1.08 to 4.08, p=0.03) (25 data sets, number of participants not stated) • children assessed at >36 months old compared to children assessed at 18-23 months (OR 4.99 95%CI 1.91 to 13.06, p=0.01) (16 data sets, number of participants not stated) (the comparison of 18-23 months and 24-36 months was not significant) Risk factors not significantly associated with vertical transmission on multivariable analysis included (25 data sets, number of participants not stated): • selection of mothers through routine screening compared to women

	identified by risk factors (OR 1.82 95%CI 0.95 to 3.48, p=0.07) and infants who were or were not lost to follow-up between birth and hepatitis C status determination (OR 1.88 95%CI 0.91 to 3.85, p=0.08) No details were reported on any factors adjusted for in the analysis Factors considered in univariate analysis only included the sample size of children assessed at follow-up, the study design (prospective vs retrospective) and the year of study (median year after 2000)
Quality appraisal	This study was assessed using the CASP checklist for systematic reviews. No quality assessment of the included studies was reported. The sample size of the populations included in the meta-analyses ranged from 14 to 739. The number of data points included in some categories for the multivariable analysis was small. No details were reported on any factors adjusted for in the analysis. As the review was specifically interested in vertical transmission according to HIV status, studies in which the mother's HIV status was not known or where results were not reported by HIV status were excluded. There was significant between studies heterogeneity in the meta-analysis for the HIV negative women.

Table 14. Cottrell et al (2013)[16]

Publication	Cottrell EB. Chou R. Wasson N. Rahman B. Guise JM. Reducing risk for mother-to-infant transmission of hepatitis C virus: a systematic review for the US Preventative Services Task Force. Ann. Intern. Med. 2013, 158:109-113
Study details	Systematic review
Study objectives	To assess effects of mode of delivery, labour management strategies and breastfeeding practices on risk of mother to child transmission
Inclusions	Studies published in English up to May 2012
Exclusions	Studies of HIV co-infected women, unless results for women not co-infected were reported separately or co-infected women made up less than 10% of the sample
Population	18 uncontrolled studies met the criteria for inclusion
Intervention	N/A
Comparator	N/A
Outcomes	No pooled analysis was performed

Mode of delivery

Risk factor	Studies	Author's conclusion
Vaginal delivery or emergency Caesarean vs elective Caesarean	4 studies (n=2,080 mother-infant pairs)	The 2 good quality studies found no statistically significant difference in risk of transmission for elective Caesarean vs vaginal birth. 2 fair quality studies had conflicting results
Vaginal delivery vs any Caesarean	11 studies (n=2,308 mother-infant pairs)	10 of the 11 studies found no statistically significant difference in risk of transmission for Caesarean vs vaginal birth (1 study was of good quality)

Internal fetal monitoring

Risk factor	Studies	Author's conclusion
Internal fetal monitoring vs no internal fetal monitoring	3 studies (n=928 mother-infant pairs)	The 2 good quality studies had conflicting results; 1 showing a statistically significant increased risk of transmission with fetal monitoring (OR 7 95%CI 1 to 36) the other showing no significantly increased risk (RR 1.2 95%CI 0.7 to 2.2). The fair quality study showed no association

OR – odds ratio; RR – relative risk

Prolonged rupture of membranes

Risk factor	Studies	Author's conclusion
Prolonged rupture of membranes vs less prolonged rupture of membranes	2 studies (n=245 mother-infant pairs)	Both studies found an association between risk of transmission and longer duration of rupture of membranes. In the good quality study, high risk of transmission was associated with membrane rupture >6 hours (OR 9 95%CI 2 to 180)

OR – odds ratio

Breastfeeding

Risk factor	Studies	Author's conclusion
Breastfeeding	14 studies (n=2,971 mother-infant pairs)	No study found a significant association between risk of transmission and breastfeeding (2 studies were of good quality)

Quality appraisal	This study was assessed using the CASP checklist for systematic reviews. There were no concerns regarding the design or conduct of the review. Similar studies were discussed as a narrative. The evidence base was conflicting in some areas and the confidence intervals around some of the significant associations were wide reducing confidence in the results. Limited details were available on the study populations. No information was provided on when the infants were tested for hepatitis C. Nine of the 14 included studies were from Europe with the remainder from Australia, the US and Japan. Studies included in the review were independently assessed as good, fair or poor quality by 2 reviewers. All of the included studies were uncontrolled with areas of concern including failure to adjust for confounders and small sample sizes.

Individual studies

Table 15. Ruiz-Extremera et al (2017)[17]

Publication	Ruiz-Extremera A. Pavón-Castillero EJ. Florido M. et al. Influence of HLA class I, HLA class II and KIRs on vertical transmission and chronicity of hepatitis C virus in children. PLOS ONE 2017, 12(2): e0172527
Study details	Prospective cohort study
Study objectives	To assess the role of immunogenetic profile in the transmission of hepatitis C from mother to child and in chronicity in children
Inclusions	Women positive for hepatitis C RNA
Exclusions	Positive test for hepatitis B or HIV, alcoholism or autoimmune disease
Population	79 mothers RNA positive for hepatitis C and their 98 children. Mothers routinely tested for hepatitis C during prenatal care at 1 hospital in Granada, Spain between 1991 and 2009. Follow-up ≥6 years[§§§§]
Intervention	N/A
Comparator	N/A
Outcomes	Mothers were tested during the third trimester (from 28 weeks to deliver), at delivery and during the post-partum period. Children were tested at birth, 2,4,6,8,10,12,18 and 24 months, 3,4,5 and 6 years Diagnosis of mother to child transmission was defined as detectable hepatitis C RNA in at least 2 blood samples Mother to child transmission was observed in 24 cases (24.4%) In multivariate analysis, risk of transmission from mother to child was decreased by: • the presence of HLA-C1 ligand in the mother (odds ratio (OR) 0.2 (95%CI 0.05 to 0.75, p=0.018) • the presence of KIR2DL3 in the child (OR 0.07 95%CI 0.004 to 1.14, p=0.062) (KIR = killer-cell immunoglobulin-like receptors) In multivariate analysis, risk of transmission was (non-significantly) increased by the presence of HLA-C2C2 ligand in mothers (OR 1.80 95%CI 0.32 to 1.05, p=0.501) Factors considered in bivariate analysis included HLA genomics for the mother (high resolution and low resolution), KIR genotyping for children and KIR/HLA ligands in mothers and children Analyses were adjusted by IL28B and viral load NB: Results regarding the risk of chronic infection in the child are not reproduced here
Quality appraisal	This study was assessed using the CASP checklist for cohort studies. The sample size was small with women recruited over an 18-year time period with a 6 year follow-up. An objective measure was used to assess hepatitis C status. Multivariate analysis was performed to determine the genetic

[§§§§] The same study population was used in Ruiz-Extremera et al (2017) and Ruiz-Extremera et al (2017). There were fewer participants included in the 2017 analysis due to the absence of plasma samples for some mothers

	factors that were independently associated with vertical transmission of hepatitis C. Analyses were adjusted by IL28B and viral load. The effect sizes described were small.

Table 16. Garcia-Tejedor et al (2015)[18]

Publication	Garcia-Tejedor A. Maiques-Montesinos V. Diago-Almela VJ. et al. Risk factors for vertical transmission of hepatitis C virus: a single center experience with 710 HCV-infected mothers. European Journal of Obstetrics & Gynecology and Reproductive Biology 2015, 194: 173-177
Study details	Retrospective cohort study
Study objectives	To assess risk factors for the perinatal transmission of hepatitis C
Inclusions	Women positive for hepatitis C RNA
Exclusions	Unknown serological status of the child
Population	710 mothers positive for hepatitis C RNA with 711 infants. Mothers attending 1 hospital in Valencia, Spain between 1986 and 2011
Intervention	N/A
Comparator	N/A
Outcomes	Mothers were screened during the first trimester and at the third trimester. Viral load results were taken from the test closest to delivery. Children were tested at 1,3,6,9,12,15,18 and 24 months Children were considered infected if they had ≥2 positive hepatitis C RNA tests 3-4 months apart after they were 2 months old and/or if a hepatitis C antibody test was still positive after 18 months The prevalence of hepatitis C for all mothers who delivered at this hospital during the study years (n=150,365) was 0.48% Mother to child transmission was observed in 17 cases (2.4%) In the multivariate analysis, risk of transmission from mother to child was significantly increased by: • use of intrapartum invasive procedures[*****] (odds ratio (OR) 10.1 95%CI 2.6 to 39.02, p=0.001) • hepatitis C viral load detectable (>650 copies/mL) (OR 9.3 (95%CI 1.11 to 78.72, p=0.04) • episiotomy[†††††] (OR 4.2 95%CI 1.24 to 14.16, p=0.02) The viral load threshold was chosen based on the most sensitive detection available during the earliest years of the study Factors not significantly associated with risk of transmission in the multivariate analysis included: • HIV coinfection (OR 3.2 95%CI 0.87 to 11.59, p=0.081) • Newborn gender female (OR 2.62 95%CI 0.91 to 7.55, p=0.075) No details were reported on any factors adjusted for in the analysis. Factors considered in univariate analysis only included mean maternal age, smoking habit, mode of acquisition (intravenous drug use vs other),

[*****] Fetal scalp blood sampling and internal electrode
[†††††] Episiotomy is a surgical cut made at the opening of the vagina during childbirth

	virus load (grouped), liver enzyme level, CDC stage of HIV, mean CD4 lymphocyte level, mean HIV viral load, antiretroviral treatment, amniocentesis, mean gestational age, mean length of rupture of membranes, length of rupture of membranes above or below 6 hours, mean length of labour, mode of delivery, fetal growth restriction, mean newborn weight and breastfeeding
Quality appraisal	This study was assessed using the CASP checklist for cohort studies. The retrospective design of the study introduces the potential for bias as information may have been missing from the medical records used as the source of the data. The number of positive cases identified over a 25 year period was small and the confidence intervals around the estimates were wide, reducing confidence in the results. An objective measure was used to assess hepatitis C status and children were followed up for 2 years. Multivariate analysis was performed to determine the risk factors that were independently associated with vertical transmission of hepatitis C. No details were reported on any factors adjusted for in the analysis.

Table 17. Delotte et al (2014)[19]

Publication	Delotte J. Barjoan EM. Berrébi A. et al. Obstetric management does not influence vertical transmission of HCV infection: results of the ALHICE group study. The Journal of Maternal-Fetal & Neonatal Medicine 2014 27(7): 664-670
Study details	Prospective cohort study
Study objectives	To investigate the impact the obstetric practice during labour and childbirth on the vertical transmission of hepatitis C
Inclusions	Pregnant women who tested positive for hepatitis C antibodies
Exclusions	Newborns monitored for less than 6 months Newborns who received a blood transfusion Children whose mothers preferred to remain anonymous
Population	214 mothers positive for hepatitis C antibodies and their 214 children attending 6 maternity hospitals in France between 1998 and 2002
Intervention	N/A
Comparator	N/A
Outcomes	Mothers were tested for hepatitis C antibodies during pregnancy (trimester not reported). A test for viral RNA was also performed and 137 mothers had circulating RNA. Children were tested at 3,6 and 12 months Children with circulating hepatitis C RNA at 12 months of the same viral genotype as their mother were considered infected and were further monitored at 18 and 24 months Mother to child transmission was observed in 12 cases (5.6%) Only univariate analysis was performed. The only statistically significant risk factor for transmission from mother to child was mother's hepatitis C viral load >6 log copies/mL (odds ratio (OR) 4 (95%CI 1.3 to 12.4, p=0.01) No details were reported on any factors adjusted for in the analysis Other factors considered in the univariate analysis included median age of the mother, discovery of hepatitis C during pregnancy, viral genotype, previous pregnancies, transfusion history, history of drug use, presence of hepatitis C in sexual partner, HIV status, hepatitis B status, coinfection with HIV and hepatitis B, gestational diabetes, alanine aminotransferase levels in pregnancy, prematurity, labour induction, mode of delivery, method of

	rupture of membranes, appearance of amniotic fluid, total duration of labour, duration of amniotic sac opening, alanine aminotransferase levels at delivery, antiseptic newborn skincare and treatments during pregnancy (for HIV coinfected mothers)
Quality appraisal	This study was assessed using the CASP checklist for cohort studies. The sample size was small and recruited over 4 year period with follow-up of up to 2 years. An objective measure was used to assess hepatitis C status and children with hepatitis C RNA were followed up for 2 years. The study included women who were positive for hepatitis C antibodies but did not have circulating RNA. The confidence intervals around the odds ratios were large reducing confidence in the results. Multivariate analysis was not performed, therefore the relationship between the different variables was not explored. No details were reported on any factors adjusted for in the analysis.

Table 18. Ruiz-Extremera et al (2011)[20]

Publication	Ruiz-Extremera A. Muñoz-Gámez JA. Salmerón-Ruiz MA. et al. Genetic variation in Interleukin 28B with respect to vertical transmission of hepatitis C virus and spontaneous clearance in HCV-infected children. Hepatology 2011, 53: 6: 1830-1838
Study details	Prospective cohort study
Study objectives	To assess the role of interleukin 28B genotype in the vertical transmission and clearance of hepatitis C
Inclusions	
Exclusions	None stated
Population	145 mothers positive for hepatitis C RNA and/or antibodies and their 185 children. 112 hepatitis C RNA positive mothers had 142 children and 33 mothers positive for hepatitis antibodies had 43 children. Mothers routinely tested for hepatitis C during prenatal care at 1 hospital in Granada, Spain between 1991 and 2009. Follow-up ≥6 years§§§§
Intervention	N/A
Comparator	N/A
Outcomes	Mothers were routinely tested during prenatal care. Children were tested at birth, 2,4,6,8,10,12,18 and 24 months, 3,4,5 and 6 years Diagnosis of mother to child transmission was defined as detectable hepatitis C RNA in at least 2 blood samples Mother to child transmission was observed in: • 20% infants (26/128) born to women positive for hepatitis C RNA and negative for HIV • 43% infants (6/14) born to women positive for hepatitis C RNA and HIV • No vertical transmission was observed in women with hepatitis C antibodies who were negative for hepatitis C RNA In multivariate analysis, risk of transmission from mother to child was significantly increased by: • high viral load (>600,000 IU/mL) (odds ratio (OR) 7.3 95%CI 1.8 to 29.4, p=0.005) • alanine transaminase (ALT) value in infants > 40 U/L (OR 5.3 95%CI 1.5 to 18.8, p=0.01) No factors were reported to be non-significant in multivariate analysis

	Other factors considered in bivariate analysis included gender of the infant, birth weight, viral genotype, mode of delivery, breastfeeding, duration of breastfeeding and mother and child's interleukin 28B genotype status NB: Results regarding the risk of chronic infection in the child are not reproduced here
Quality appraisal	This study was assessed using the CASP checklist for cohort studies. The study sample size was small with women recruited over an 18-year time period and children followed up for 6 years. An objective measure was used to assess hepatitis C status. Multivariate analysis was performed to determine the genetic factors that were independently associated with vertical transmission of hepatitis C. No details were reported on any factors adjusted for in the analysis. The confidence intervals around the odds ratios were large reducing confidence in the results.

Data extraction and quality assessment for studies relevant to criterion 4

Key question 3: What is the diagnostic accuracy of second, third and fourth generation antibody tests for the detection of hepatitis C?

No studies met the criteria for inclusion.

Data extraction and quality assessment for studies relevant to criterion 9

Key question 4: What is the reported effectiveness of direct acting antivirals (DAAs) in pregnancy for the prevention of hepatitis C vertical transmission and hepatitis C associated morbidity in pregnant women?

No studies met the criteria for inclusion.

Key question 5: What is the reported effectiveness of direct acting antivirals (DAAs) in children with vertically acquired hepatitis C on hepatitis C associated morbidity and cure?

No studies met the criteria for inclusion.

Appendix 4 – UK NSC reporting checklist for evidence summaries

All items on the UK NSC Reporting Checklist for Evidence Summaries have been addressed in this report. A summary of the checklist, along with the page or pages where each item can be found in this report, is presented in Table 19.

Table 19. UK NSC reporting checklist for evidence summaries

	Section	Item	Page no.
1.	TITLE AND SUMMARIES		
1.1	Title sheet	Identify the review as a UK NSC evidence summary.	Title page
1.2	Plain English summary	Plain English description of the executive summary.	5
1.3	Executive summary	Structured overview of the whole report. To include: the purpose/aim of the review; background; previous recommendations; findings and gaps in the evidence; recommendations on the screening that can or cannot be made on the basis of the review.	7
2.	INTRODUCTION AND APPROACH		
2.1	Background and objectives	Background – Current policy context and rationale for the current review – for example, reference to details of previous reviews, basis for current recommendation, recommendations made, gaps identified, drivers for new reviews	10
		Objectives – What are the questions the current evidence summary intends to answer? – statement of the key questions for the current evidence summary,	14

		criteria they address, and number of studies included per question, description of the overall results of the literature search. Method – briefly outline the rapid review methods used.	16
2.2	Eligibility for inclusion in the review	State all criteria for inclusion and exclusion of studies to the review clearly (PICO, dates, language, study type, publication type, publication status etc.) To be decided *a priori*.	17
2.3	Appraisal for quality/risk of bias tool	Details of tool/checklist used to assess quality, eg QUADAS 2, CASP, SIGN, AMSTAR.	20
3.	SEARCH STRATEGY AND STUDY SELECTION (FOR EACH KEY QUESTION)		
3.1	Databases/ sources searched	Give details of all databases searched (including platform/interface and coverage dates) and date of final search.	20
3.2	Search strategy and results	Present the full search strategy for at least one database (usually a version of Medline), including limits and search filters if used. Provide details of the total number of (results from each database searched), number of duplicates removed, and the final number of unique records to consider for inclusion.	Appendix 1
3.3	Study selection	State the process for selecting studies – inclusion and exclusion criteria, number of studies screened by title/abstract and full text, number of reviewers, any cross checking carried out.	16
4.	STUDY LEVEL REPORTING OF RESULTS (FOR EACH KEY QUESTION)		
4.1	Study level reporting, results and risk of bias	For each study, produce a table that includes the full citation and a summary of the data relevant to the question (for example, study size, PICO, follow-up	Study level reporting: Appendix 3 Quality assessment: Appendix 3

	assessment	period, outcomes reported, statistical analyses etc.). Provide a simple summary of key measures, effect estimates and confidence intervals for each study where available. For each study, present the results of any assessment of quality/risk of bias.	
5.	QUESTION LEVEL SYNTHESIS		
5.1	Description of the evidence	For each question, give numbers of studies screened, assessed for eligibility, and included in the review, with summary reasons for exclusion.	21,24,31,34,36
5.2	Combining and presenting the findings	Provide a balanced discussion of the body of evidence which avoids over reliance on one study or set of studies. Consideration of four components should inform the reviewer's judgement on whether the criterion is 'met', 'not met' or 'uncertain': quantity; quality; applicability and consistency.	29,32,37
5.3	Summary of findings	Provide a description of the evidence reviewed and included for each question, with reference to their eligibility for inclusion. Summarise the main findings including the quality/risk of bias issues for each question. Have the criteria addressed been 'met', 'not met' or 'uncertain'?	22,25,31,34,36
6.	REVIEW SUMMARY		
6.1	Conclusions and implications for policy	Do findings indicate whether screening should be recommended? Is further work warranted? Are there gaps in the evidence highlighted by the review?	38
6.2	Limitations	Discuss limitations of the available evidence and of the review methodology if relevant.	39

Appendix 5 – UK NSC Evidence Map

Summary of the clinical and cost-effectiveness of antenatal and postnatal hepatitis C virus (HCV) screening programmes

A literature search performed by the UK NSC in January 2018 found that there have been no RCTs or observational studies comparing vertical transmission rates of HCV in pregnant women screened compared to those not screened. Nor have there been any RCTs or observational studies comparing clinical outcomes in the screened and unscreened pregnant women and their infants.[1] Similarly, no studies have explored postnatal screening. Without direct evidence of the clinical benefits of universal HCV screening compared to no or other prevention approaches, a clear evaluation of the clinical or cost-effectiveness of antenatal or postnatal HCV screening programmes is unlikely to be possible. In 2013, the US Preventive Services Task Force (USPSTF) considered the evidence related to HCV screening including evidence related to pregnant women. They recommended screening for persons with high risk of infections but there was no recommendation for all pregnant women.[2] The risk factors were past or current injection drug use, blood transfusion before 1992, long-term haemodialysis, being born to an HCV-infected mother, incarceration, intranasal drug use, getting an unregulated tattoo, and other percutaneous exposures. Likewise, the Centers for Disease Control and Prevention (CDC) and the American College of Obstetricians and Gynecologists (ACOG) only recommend risk-based screening for HCV in pregnant women.[3]

In the absence of analytical studies, there have been some economic modelling evaluations and systematic reviews of these, as well as observational studies exploring detection rates in screening. Four systematic reviews of economic evaluations concluded that HCV screening in pregnancy was not cost-effective,[4 5] may not be good value for money,[6] and that no screening dominated screening strategies.[7] These estimates contain a high degree of uncertainty as the clinical benefits to women and children of screening are unknown. Additionally, as the current treatments are contraindicated in pregnancy, the treatments modelled in the economic evaluations were to treat mothers (and their children in one study) following delivery. Of the individual evaluations, in the US, Plunkett et al. (2005) compared routine screening followed by treatment for mothers and children after the completion of pregnancy, or routine screening followed by elective caesarean section delivery and treatment, versus no screening.[8] Assessing lifetime costs and quality-adjusted life years (QALYs) for mother and child, the authors found that no screening was more effective and less costly than routine screening (dominated), even when perinatal transmission was increased to 12% and HCV prevalence to 10%. Adding caesarean section to the screening strategy revealed a cost-effectiveness ratio of $1,170,000 per QALY.[8] Similarly, in the Netherlands, Urbanus et al. (2013) found that screening of all pregnant women with treatment given two years after diagnosis compared with no screening was unlikely to be cost-effective (€52,473 per life year gained) when assessing the costs in pregnant women only (not children).[9] By contrast, in the UK, Selvapatt et al. (2015) found that universal antenatal screening and treatment after delivery was likely to be cost-effective

(£2,400 per QALY) compared with no screening when assessing costs in pregnant women only.[10] The authors also projected that the newer direct-acting antiviral treatments in women would also be cost-effective (£9,139 per QALY). In addition to the exclusion of the costs or benefits for testing and treatment of the children, the authors acknowledged that the study population, which was based in in London, had an overrepresented migrant population.[10]

The observational studies have reported on testing only. In these programmes, treatment for women would be after delivery and their children would be followed up. Waruingi et al. (2016) found that the sensitivity of risk-based selective screening (as assessed by an obstetricians' screening questionnaire) during pregnancy was 0.85 (0.42 to 0.99) and the specificity was 0.52 (0.45 to 0.58), therefore risk-based screening may under-detect cases.11 Three observational studies found that around 20% to 30% of screen-detected HCV positive women have no risk factors. 12-14 However, two studies found that universal screening did not detect more pregnant women with HCV than risk-based screening.12 15 Finally, Lambert et al. (2013) found a high uptake rate of 98.4% for serology-based antenatal HCV screening,13 and Kuncio et al. (2016) found that of all the children born to HCV screen positive pregnant women, 84% were lost to follow up and only 16% were tested.16 As none of these observational studies follow populations to clinical outcomes, no conclusions can be reached.

Evidence map references

1. Chou R, Cottrell E, Wasson N, et al. Screening for Hepatitis C Virus Infection in Adults. Comparative Effectiveness Reviews. Rockville (MD): Agency for Healthcare Research and Quality (US), 2012.
2. Moyer VA, on behalf of the USPSTF. Screening for hepatitis c virus infection in adults: U.s. preventive services task force recommendation statement. *Annals of Internal Medicine* 2013;159(5):349-57. doi: 10.7326/0003-4819-159-5-201309030-00672
3. Hughes BL, Page CM, Kuller JA. Hepatitis C in pregnancy: screening, treatment, and management. *American Journal of Obstetrics & Gynecology* 2017;217(5):B2-B12. doi: 10.1016/j.ajog.2017.07.039
4. Hahne SJ, Veldhuijzen IK, Wiessing L, et al. Infection with hepatitis B and C virus in Europe: a systematic review of prevalence and cost-effectiveness of screening. *BMC infectious diseases* 2013;13:181. doi: 10.1186/1471-2334-13-181 [published Online First: 2013/04/20]
5. Coretti S, Romano F, Orlando V, et al. Economic evaluation of screening programs for hepatitis C virus infection: evidence from literature. *Risk management and healthcare policy* 2015;8:45-54. doi: 10.2147/rmhp.s56911 [published Online First: 2015/05/12]
6. Coward S, Leggett L, Kaplan GG, et al. Cost-effectiveness of screening for hepatitis C virus: a systematic review of economic evaluations. *BMJ Open* 2016;6(9) doi: 10.1136/bmjopen-2016-011821
7. Geue C, Wu O, Xin Y, et al. Cost-Effectiveness of HBV and HCV Screening Strategies--A Systematic Review of Existing Modelling Techniques. *PloS one* 2015;10(12):e0145022. doi: 10.1371/journal.pone.0145022 [published Online First: 2015/12/23]
8. Plunkett BA, Grobman WA. Routine hepatitis C virus screening in pregnancy: A cost-effectiveness analysis. *American Journal of Obstetrics and Gynecology* 2005;192(4):1153-61. doi: https://doi.org/10.1016/j.ajog.2004.10.600

9. Urbanus AT, van Keep M, Matser AA, et al. Is Adding HCV Screening to the Antenatal National Screening Program in Amsterdam, The Netherlands, Cost-Effective? *PloS one* 2013;8(8):e70319. doi: 10.1371/journal.pone.0070319
10. Selvapatt N, Ward T, Bailey H, et al. Is antenatal screening for hepatitis C virus cost-effective? A decade's experience at a London centre. *Journal of hepatology* 2015;63(4):797-804. doi: 10.1016/j.jhep.2015.05.015 [published Online First: 2015/05/31]
11. Waruingi W, Mhanna MJ, Kumar D, et al. Hepatitis C Virus universal screening versus risk based selective screening during pregnancy. *Journal of neonatal-perinatal medicine* 2015;8(4):371-8. doi: 10.3233/npm-15915024 [published Online First: 2016/02/03]
12. Diab-Elschahawi M, Dosch V, Honsig C, et al. Evaluation of a universal vs a targeted hepatitis C virus screening strategy among pregnant women at the Vienna University Hospital. *American journal of infection control* 2013;41(5):459-60. doi: 10.1016/j.ajic.2012.06.003 [published Online First: 2012/10/23]
13. Lambert J, Jackson V, Coulter-Smith S, et al. Universal antenatal screening for hepatitis C. *Irish medical journal* 2013;106(5):136-9. [published Online First: 2013/08/07]
14. McDermott CD, Moravac CC, Yudin MH. The effectiveness of screening for hepatitis C in pregnancy. *Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC* 2010;32(11):1035-41. doi: 10.1016/s1701-2163(16)34710-7 [published Online First: 2010/12/24]
15. Martyn F, Phelan O, O'Connell M. Hepatitis C: is there a case for universal screening in pregnancy? *Irish medical journal* 2011;104(5):144-6. [published Online First: 2011/07/09]
16. Kuncio DE, Newbern EC, Johnson CC, et al. Failure to Test and Identify Perinatally Infected Children Born to Hepatitis C Virus-Infected Women. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2016;62(8):980-5. doi: 10.1093/cid/ciw026 [published Online First: 2016/01/23]

References

[1] UK National Screening Committee. Commissioning brief for antenatal screening for hepatitis C virus. December 2017
[2] Thorne C. Knowledge update on screening for hepatitis C virus in pregnancy. February 2011
[3] Public Health England. Hepatitis C in England. 2018 report. Available from https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/693917/HCV_in_England_2018.pdf (accessed March 2018)
[4] Pembrey L. Newell ML. Peckham C. Is there a case for hepatitis C infection screening in the antenatal period? J. Med. Screen. 2003, 10: 161-168
[5] Indolfi G. Hierro L. Dezsofi A. et al. Treatment of Chronic Hepatitis C Virus Infection in Children. A Position Paper by the Hepatology Committee of European Society of Paediatric Gastroenterology, Hepatology and Nutrition. Journal of Pediatric Gastroenterology & Nutrition 2017, 28:28
[6] Hutchinson SJ. Goldberg DJ. King M. et al. Hepatitis C virus among childbearing women in Scotland: prevalence, deprivation and diagnosis. Gut 2004, 53(4): 593-8
[7] Benova L. Mohamoud YA. Calvert C. Abu-Raddad LJ. Vertical transmission of hepatitis C virus: systematic review and meta-analysis. Clinical Infectious Diseases 2014, 59(6): 765-773
[8] Mok J. Pembrey L. Tovo PA. Newell ML. When does mother to child transmission of hepatitis C virus occur. Arch. Dis. Child Fetal. Neonatal Ed. 2005, 90(2): F156-F160
[9] Lin HH. Kao JH. Effectiveness of second and third-generation immunoassays for the detection of hepatitis C virus infection in pregnant women. Journal of Obstetric and Gynaecology Research 2000, 26(4): 265-70
[10] Schwarz KB. Gonzalez-Peralta RP. Murray KF. et al. The combination of ribavirin and peginterferon is superior to peginterferon and placebo for children and adolescents with chronic hepatitis C. Gastroenterology 2011, 140(2): 450-458
[11] Jakobsen JC. Nielsen EE. Feinberg J. et al. Direct-acting antivirals for chronic hepatitis C. Cochrane Database of Systematic Reviews 2017, Issue 9, Art. No.: CD012143.DOI: 10.1002/14651858.CD012143.pub3
[12] UK National Screening Committee. The clinical and cost-effectiveness of antenatal and postnatal hepatitis C virus (HCV) screening programmes: evidence map summary. April 2018
[13] Cortina-Borja M. Williams D. Peckham CS. Bailey H. Thorne C. Hepatitis C virus seroprevalence in pregnant women delivering live-born infants in North Thames, England in 2012. Epidemiol. Infect. 2016, 144: 627-634
[14] Orkin C. Jeffery-Smith A. Foster GR. Tong CYW. Retrospective hepatitis C seroprevalence screening in the antenatal setting – should we be screening antenatal women? BMJ Open 2016, 6: e010661
[15] Selvapatt N. Ward T. Bailey H. et al. Is antenatal screening for hepatitis C virus cost-effective? A decade's experience at a London centre. Journal of Hepatology 2015, 63: 797-804
[16] Cottrell EB. Chou R. Wasson N. Rahman B. Guise JM. Reducing risk for mother-to-infant transmission of hepatitis C virus: a systematic review for the US Preventative Services Task Force. Ann. Intern. Med. 2013, 158:109-113
[17] Ruiz-Extremera A. Pavón-Castillero EJ. Florido M. et al. Influence of HLA class I, HLA class II and KIRs on vertical transmission and chronicity of hepatitis C virus in children. PLOS ONE 2017, 12(2): e0172527

[18] Garcia-Tejedor A. Maiques-Montesinos V. Diago-Almela VJ. et al. Risk factors for vertical transmission of hepatitis C virus: a single center experience with 710 HCV-infected mothers. European Journal of Obstetrics & Gynecology and Reproductive Biology 2015, 194: 173-177
[19] Delotte J. Barjoan EM. Berrébi A. et al. Obstetric management does not influence vertical transmission of HCV infection: results of the ALHICE group study. The Journal of Maternal-Fetal & Neonatal Medicine 2014 27(7): 664-670
[20] Ruiz-Extremera A. Muñoz-Gámez JA. Salmerón-Ruiz MA. et al. Genetic variation in Interleukin 28B with respect to vertical transmission of hepatitis C virus and spontaneous clearance in HCV-infected children. Hepatology 2011, 53: 6: 1830-1838
[21] Bernstein HB. Dunkelberg JC. Leslie KK. Hepatitis C in pregnancy in the era of direct-acting antiviral treatment: potential benefits of universal screening and antepartum therapy. Clinical Obstetrics and Gynecology 2018, 61 (1): 146-156
[22] Hashmi MA. Cheema HA. Effectiveness and safety of sofosbuvir in treatment-näive children with hepatitis C infection. Journal of the College of Physicians and Surgeons Pakistan 2017, 27(7): 423-426