UK National Screening Committee

Antenatal screening for HSV-1 and HSV-2 infection to prevent neonatal herpes infection

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

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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

Screening pregnant women for herpes simplex virus (HSV) aims to prevent the herpes infection being passed on to the baby. There are 2 types of HSV. HSV-1 usually causes cold sores but genital infection is also possible. HSV-2 is a sexually transmitted infection.

Herpes in a newborn baby is rare but serious. About 1 in 5 newborn babies with herpes die. About half of the newborn babies that survive have lasting nervous system problems.

In most cases, HSV is passed from the mother to baby during birth. Women who get an HSV infection for the first time late in pregnancy have the greatest risk of passing HSV to their baby. A mother can still pass HSV to their baby even if they do not have any symptoms themselves.

This document looks at new evidence about screening pregnant women for HSV published between October 2005 and February 2018.

The UK National Screening Committee (UK NSC) published its last review in 2006. This recommended against introducing a screening programme for genital herpes in pregnant women in the UK. The last review found no evidence that screening pregnant women to identify those at risk of getting HSV infection prevents herpes infection in the baby. The last review also found limited evidence that interventions successfully prevent women from passing the herpes infection to their baby.

The current review looked at some key questions:

1. how many cases of newborn babies with herpes are there in the UK?
2. how many pregnant women in the UK test positive for HSV-1 or HSV-2?
3. how accurate are screening tests for HSV-1 and HSV-2 in pregnant women?
4. is there a way of reducing the risk that pregnant women will be infected with HSV during pregnancy?
5. is there an effective way of reducing the risk that a mother with HSV will pass the infection to her baby?

This UK NSC still cannot recommend screening all pregnant women for HSV. 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 HSV-1 and HSV-2
- the accuracy of screening tests for HSV-1 in pregnant women
- the accuracy of screening tests for HSV-2 in UK pregnant women
- the effectiveness of interventions to prevent pregnant women getting the infection or passing the infection on to their baby.

Executive summary

Purpose of the review

This document reviews the evidence on antenatal screening for HSV-1 and HSV-2 infection to prevent neonatal herpes infection.

Background

There are 2 strains of herpes simplex virus (HSV). HSV-1 usually presents as oral (oro-labial) herpes with cold sores on the lips, but can also cause genital HSV-1 infection. In adults, HSV-2 is typically sexually transmitted and causes genital lesions such as sores or blisters on the skin.

Neonatal herpes is a rare but potentially serious infection that is fatal in about 20% of cases. Around half of the neonates that survive have persisting neurological impairment. In the UK, around half of neonatal herpes infections reported were due to HSV-1. HSV can be passed from a mother who has genital herpes to her baby during pregnancy or birth. HSV can also be passed on postnatally through contact between a newborn and an infected individual. The majority of neonatal herpes cases (85%) result from exposure to infected genital secretions during vaginal delivery.

Serologic screening for HSV (by detecting HSV antibodies from a blood sample) can identify women who do not have HSV infection* (seronegative women) and women with a prior HSV infection (seropositive women).

The greatest risk for transmission of HSV from mother to baby is when a seronegative mother acquires a primary genital herpes infection in the third trimester of pregnancy, as the baby is likely to be born before the mother has produced and passed on protective maternal antibodies. Women who have a recurrent genital herpes infection during pregnancy

*Women who are yet to developed antibodies in response to a recent HSV infection will also be identified as seronegative

can also pass on the infection to their baby, but the risk of transmission is much lower in this group. Transmission can occur from both symptomatic and asymptomatic mothers, and about two-thirds of infected infants are born to women with no clinical evidence of disease and mostly with no history of genital infection.

Focus of the review

The aim of an antenatal population screening programme for HSV-1 and HSV-2 would be to prevent neonatal herpes infection. This review looks for evidence of effective interventions to reduce the risk of acquisition of HSV in women who do not have HSV infection (seronegative women), and interventions for reducing the vertical transmission of HSV from women with past exposure to the virus (seropositive women).

This evidence summary includes studies published between October 2005 and February 2018. It considers 5 key questions relating to incidence and prevalence in the UK, the test and the intervention:

1. what is the incidence of neonatal herpes in the UK?
2. what is the seroprevalence of HSV-1 and HSV-2 in pregnant women in the UK?
3. what is the accuracy of serologic screening for HSV-1 and HSV-2 in pregnancy?
4. is there an effective management strategy to reduce the risk of HSV acquisition in seronegative pregnant women?
5. is there an effective intervention for reducing vertical transmission of HSV from mother to child?

Recommendation under review

The current UK NSC policy is that systematic population screening for genital herpes in pregnant women is not recommended. The previous UK NSC external review was published in 2006 and concluded that there was “no evidence that universal serologic screening in pregnancy to identify women at risk of new infections will effectively decrease the incidence of neonatal infections in the perinatal period”. The 2006 review also concluded that there was “limited evidence that drug treatment or the performance of elective Caesarean section in seropositive women or those with a history of genital infection reduces transmission of neonatal infections to infants born to this group of women.”

Findings and gaps in the evidence of this review

The current review found that the volume, quality and direction of new evidence published since October 2005 does not indicate that there have been any significant changes in the evidence base since the previous review. Key areas of concern relate to:

- there are uncertainties about the seroprevalence of HSV-1 and HSV-2 in UK pregnant women
- there is an absence of evidence about the performance of screening tests for HSV-1 in pregnant women
- there are uncertainties about the performance of screening tests for HSV-2 in UK pregnant women, particularly around the number of false positive tests that might be expected
- there is some evidence that intervention (eg knowledge of a sex partner's HSV status) can reduce risky behaviours in women seronegative for HSV-2. There is also some evidence that intervention (eg oral antiviral therapy) can reduce risk factors for vertical transmission for women with HSV infection. However the resulting impact on neonatal infection was not established.

Recommendations on screening

The current recommendation not to introduce a UK systematic population screening programme for HSV-1 and HSV-2 infection should be retained.

Limitations

A limitation for this review is the lack of evidence specific to pregnant women, particularly around the UK prevalence of HSV and performance of screening tests for HSV-1.

Introduction and approach

This evidence summary reviews antenatal screening for HSV-1 and HSV-2 infection against selected UK National Screening Committee criteria. The aim of an antenatal population screening programme for HSV-1 and HSV-2 would be to prevent neonatal herpes infection. The review looks for evidence of effective interventions to prevent neonatal herpes transmission from those who could be identified through antenatal screening; women at risk of acquiring HSV infection (seronegative women), and those with prior HSV infection (seropositive women).

Background

Neonatal herpes is a herpes simplex virus (HSV) infection in a newborn. There are 2 strains of HSV. HSV-1 is usually acquired in early life presenting as oral (oro-labial) herpes developing as cold sores on the lips. However genital HSV-1 infection also occurs[1] and HSV-1 is now the most common cause of genital herpes in the UK[2]. HSV-2 is typically sexually transmitted and causes genital lesions such as sores or blisters on the skin[3]. In the UK, around half of neonatal herpes infections reported were due to HSV-1[3].

Although rare, neonatal herpes is a potentially serious viral infection[3]. In1 UK study[4] 9 of 19 babies (47%) included in a clinical review of cases died. About 50% of survivors have persisting moderate or severe neurological impairment[3]. About a third of neonates with herpes present with isolated lesions of the skin, eye or mouth, a third with localised central nervous system involvement such as encephalopathy with or without skin lesions and a third with disseminated disease involving multiple organs[3].

Serologic screening for HSV (by detecting HSV antibodies from a blood sample) can identify women who do not have HSV infection[†] (seronegative women) and women with a prior HSV infection (seropositive women).

[†] Women who are yet to develop antibodies in response to a recent HSV infection will also be identified as seronegative

In most cases (85%) vertical transmission from mother to neonate occurs following exposure to infected genital secretions during vaginal delivery. About 5% of neonatal infections result from intrauterine infection and about 10% occur postnatally through contact with infected individuals[3]. The greatest risk of vertical transmission occurs when a seronegative woman acquires a primary genital herpes infection in the third trimester of pregnancy, as the baby is likely to be born before the mother has produced and passed on protective maternal antibodies[3]. Vertical transmission can also occur following a recurrent genital herpes infection during pregnancy, but the risk of transmission is much lower in this group[3]. Transmission to the neonate can occur following both a symptomatic recurrence in the mother and episodes of asymptomatic virus shedding[3]. About two-thirds of infected infants are born to women with no clinical evidence of disease and mostly with no history of genital infection[3].

The 2006 UK NSC external review considered the evidence for antenatal population screening for HSV-1 and HSV-2 infection against the UK NSC programme appraisal criteria[3]. This reported that the incidence of HSV-1 in childhood has been falling in England and Wales with an increase in adult infection. The study cited in the 2006 review (Vyse et al 2000[5]) reported the seroprevalence of HSV-1 as 54% in a general population of women aged 25 to 30 years (1994-95 data). The same study reported an HSV-2 seroprevalence of 5.1% for a general population of women aged 16 to 69 years. The prevalence of HSV was reported to vary widely within subgroups of the population[3].

About 60 UK neonatal herpes cases were identified in 2004-2005 with a prevalence of 4 per 100,000 live births[3]. This was an increase from a previously reported prevalence of 1.65 per 100,000 live births from 76 cases identified between 1986 and 1991[3].

The 2006 UK NSC review discussed the natural history of HSV, reporting that women who have a first episode of disease are more likely to have cervical infection and to shed larger quantities of virus for a longer period than women with a recurrence of genital herpes. The 2006 review also stated that after a primary infection the virus remains latent, with recurrent viral reactivations that can be symptomatic or asymptomatic[3].

Screening for HSV uses serological methods to detect antibodies to the virus. The 2006 UK NSC review described serological tests for HSV-2 as being relatively accurate but discussed the likelihood of false positive tests[3]. Details of test performance were not reported.

With regards to management strategies, the 2006 UK NSC review reported that the risk of virus transmission to a neonate is greatest if a seronegative woman has a first episode of genital herpes infection near to delivery, prior to developing protective antibodies[3]. The 2006 review stated that seronegative women could be offered advice about potential ways to reduce their risk of acquiring the virus such as using a condom or only having intercourse with partners known to be free of infection. However, the 2006 review also stated that there was no evidence about whether this is likely to be an effective approach to prevention[3].

The 2006 UK NSC review reported that seropositive women could be tested for recurrent infection. The risk of neonatal infection has been associated with long duration of rupture of the membranes and the use of invasive obstetrical procedures such as fetal scalp electrodes[3]. The 2006 review discussed the potential for offering antiviral therapy to reduce shedding or the use of elective Caesarean section to reduce the risk of transmission. However, there was considered to be limited evidence for the effectiveness of these strategies[3].

Current policy context and previous reviews

The current UK NSC policy is that systematic population screening for genital herpes in pregnancy is not recommended. The previous UK NSC external review of screening for HSV-1 and HSV-2 infection considered literature published up to September 2006[3]. This concluded that there was:

- “no evidence that universal serologic screening in pregnancy to identify women at risk of new infections will effectively decrease the incidence of neonatal infections in the perinatal period
- limited evidence that drug treatment or the performance of elective Caesarean section in seropositive women or those with a history of genital infection reduces transmission of neonatal infections to infants born to this group of women.”

Guidance on reducing the risk of transmission of HSV at birth was produced in 2014 by the British Association for Sexual Health and HIV and the Royal College of Obstetricians and Gynaecologists[6].

The United States Preventative Services Task Force (USPSTF) updated their evidence review for screening for genital herpes in December 2016[7], recommending against routine serologic screening in asymptomatic adolescents and adults, including those who are pregnant.

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 incidence of neonatal herpes in the UK? 2. What is the seroprevalence of HSV-1 and HSV-2 in pregnant women in the UK?	1 7
	THE TEST		
4	There should be a simple, safe, precise and validated screening test.	3. What is the accuracy of serologic screening for HSV-1 and HSV-2 in pregnancy?	1
	THE INTERVENTION		
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	4. Is there an effective management strategy to reduce the risk of HSV acquisition in seronegative pregnant women? 5. Is there an effective	1

	Criterion	Key questions	Studies Included
	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.	intervention for reducing vertical transmission of HSV from mother to child?	2

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 about study inclusion 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. Only peer-reviewed studies published in English between October 2005 and February 2018 were eligible for consideration in the review.

A total of 713 references were identified and sifted by an information scientist by title and abstract for potential relevance to the review. 105 titles and abstracts were reviewed by an SPH reviewer for further appraisal and possible inclusion in the final review.

Overall, 41 studies were identified as possibly relevant during title and abstract sifting and were further assessed at full text.

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 incidence of neonatal herpes in the UK?	Neonates	Neonatal herpes	N/a	N/a	Confirmed cases of neonatal herpes	Cross sectional studies, cohort studies, national registry data and systematic reviews of these studies Studies carried out within the UK should be prioritised. Western populations that are analogous to the UK can also be included	Case reports Case series Narrative reviews
2. What is the seroprevalence of HSV-1 and HSV-2 in pregnant women in the UK?	General pregnant population	HSV in pregnant women	N/a	N/a	Confirmed cases of HSV infection	Cross sectional studies, cohort studies, national registry data and systematic reviews of these studies Studies carried out within the UK should be prioritised. Western populations that are analogous to the UK can also be included	Case reports Case series Narrative reviews
3. What is the accuracy of serologic testing for HSV-1 and HSV-2 in	General pregnant population	HSV in pregnant women	Type specific serologic testing for HSV-1 and HSV-2. Type	Western blot	Measures of clinical validity of screening tests	Studies in randomly assigned or consecutively enrolled populations, systematic reviews	Case reports Case series Case control studies Narrative

pregnancy?			specific or combined testing				reviews Non-peer reviewed literature
4. Is there an effective management strategy to reduce the risk of HSV acquisition in seronegative pregnant women?	HSV seronegative pregnant women	HSV in pregnant women	Information and/or other interventions to prevent infection	No intervention or placebo	Reduced maternal HSV infection and reduced neonatal infection	RCTs, controlled clinical trials, observational studies with a comparison group (eg comparative cohort studies) and systematic reviews	Case reports Case series Narrative reviews Non-peer reviewed literature
5. Is there an effective intervention for reducing vertical transmission of HSV from mother to child?	Pregnant women with HSV infection Seropositive pregnant women	Neonatal herpes	Any intervention eg antiviral drugs, Caesarean section	Normal care	Infection free newborn Reduction in sequelae	RCTs, controlled clinical trials, observational studies with a comparison group (eg comparative cohort studies) and systematic reviews	Case reports Case series Narrative reviews Non-peer reviewed literature

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.
- diagnostic accuracy studies: Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool
- RCTs: Cochrane Collaboration's "Risk of Bias" Tool
- 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 for evidence published since 2005. 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 incidence of neonatal herpes in the UK?

The 2006 UK NSC evidence review reported that about 60 UK neonatal herpes cases were identified in 2004-2005 with a prevalence of 4 per 100,000 live births[3]. This was an increase from a previously reported prevalence of 1.65 per 100,000 live births from 76 cases identified between 1986 and 1991[3].

Eligibility for inclusion in the review

The inclusion criteria for this question are summarised briefly below:

- population – neonates
- intervention – N/a
- comparator – N/a
- outcomes – confirmed cases of neonatal herpes
- studies – cross sectional studies, cohort studies, national registry data and systematic reviews of these. Studies carried out within the UK should be prioritised.

Description of the evidence

Database searches yielded 105 results, of which 16 were judged to be relevant to this question and 4 abstracts met the criteria for full text review. After review of the full texts, 1 study reporting UK incidence was included. The other 3 studies were excluded after full text review because they did not provide information on the incidence of neonatal herpes in the UK.

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.

One study (Batra et al 2014[4]) estimated the incidence of neonatal herpes from cases identified from a geographically defined, mostly urban UK population, between 2006 and 2012. The precise geographical location was not specified. There were 10 cases of neonatal herpes from 57,291 live births; an incidence of 17.5 per 100,000 live births (95%CI 8.4 to 32.1). The same study described 19 neonatal herpes cases born at 1 UK centre between 2006 and 2013. Of these 9 were HSV-1 cases, 8 were HSV-2 cases and 2 were cases of unknown serotype. The 4 cases that presented within 48 hours of birth were considered to represent either in utero or early perinatal infection. The remaining cases presented between 3 and 14 days after birth.

The study was assessed using the JBI critical appraisal checklist for studies reporting prevalence data. The areas of concern related to the small sample size and limited details about the study population. The number of cases over the 6 year time period was small (n=10) and the confidence intervals around the incidence are wide reducing confidence in the estimate. As the precise geographical location is not specified, it is not clear if the higher incidence in this population would apply to the UK as a whole.

Question 2 – What is the seroprevalence of HSV-1 and 2 in pregnant women in the UK?

The 2006 UK NSC review did not report a specific figure for the seroprevalence of HSV-1 and HSV-2 in UK pregnant women. However the 2006 review stated that the incidence of HSV-1 in childhood has been falling in England and Wales with an increase in adult infection. The 2006 review cited a study[5] on the seroprevalence of HSV-1 and HSV-2 in the general UK population. This study reported an HSV-1 seroprevalence of 54% for women aged 25 to 30 years and an HSV-2 seroprevalence of 5.1% for women aged 16 to 69 years[5].

Eligibility for inclusion in the review

The inclusion criteria for this question are summarised briefly below:

- population – general pregnant population
- intervention – N/a
- comparator – N/a
- outcomes – confirmed cases of HSV infection
- studies – cross sectional studies, cohort studies, national registry data and systematic reviews of these. Studies carried out within the UK should be prioritised. Studies carried out in Western populations that are analogous to the UK can also be included.

Description of the evidence

Database searches yielded 105 results, of which 26 were judged to be relevant to this question and 13 abstracts met the criteria for full text review. After review of the full texts, 7 studies were included.

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

- 3 studies reporting prevalence for a general rather than pregnant population
- 1 study where the population was not analogous to the UK
- 1 study that did not report seroprevalence
- 1 older study from a non-UK country for which more recent data were available.

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.

No studies reporting the UK seroprevalence of HSV-1 or HSV-2 in pregnant women were identified. Therefore 7 studies on the seroprevalence of HSV-1 and HSV-2 in pregnant women in other Western populations analogous to the UK were included. The seroprevalence figures reported in these studies are summarised in Table 3. Further details about the studies are provided in the Appendix 3 tables.

The reported seroprevalence rates varied between the different countries. For HSV-1 this ranged from 45% in a Finnish study[9] to 91% in an Italian

study[8]. For HSV-2 the seroprevalence ranged from 9% in a Swedish study[12] to 22% in a US study[14].

Table 3. Summary of HSV seroprevalence in pregnant women.

Country	Population	HSV-1 seroprevalence	HSV-2 seroprevalence	Study
Italy	91 samples from a university serum bank collected between 2003 and 2005	91.2% (CI not reported)	9.9% (CI not reported)	Marchi et al (2017)[8]
Finland	600 samples from a national biorepository (200 samples per year for 1992, 2002‡ and 2012)	1992: 69.5% (95%CI 62.6 to 75.8) 2012: 45.0% (95%CI 38.0 to 52.2)	1992: 17.5% (95%CI 12.5 to 23.5) 2012: 11.0% (95%CI 7.0 to 16.2)	Puhakka et al (2016)[9]
Switzerland	1,030 women attending an antenatal clinic from 2004 to 2007	79.4% (95%CI 79.6 to 81.9)	21.2% (95%CI 18.7 to 23.7)	Kucera et al (2012)[10]
Germany	200 women delivering at 1 hospital between 1999 and 2000	82.0% (95%CI 76.0 to 87.1)	18.0% (95%CI 12.9 to 24.0)	Sauerbrei et al (2011)[11]
Sweden	229 women attending an antenatal clinic during 2002	---	9.0% (95%CI 6.3 to 12.8)	Berntsson et al (2009)[12]
Australia	1,371 women attending an antenatal clinic from 2000 to 2002	---	13.6% (95%CI 11.9 to 15.6)	Sasadeusz et al (2008)[13]
USA	626 women participating in a national survey and clinical examination from 1999 to 2002	63% (CI not reported)	22% (95%CI 16 to 31)	Xu et al (2007)[14]

‡ Data for 2002 was only provided graphically in the study publication and is not reproduced here

The studies were assessed using the JBI critical appraisal checklist for studies reporting prevalence data. All of the studies had small sample sizes (ranging from 91 to 1,371). Although all of the studies were from Western populations, some had limited details about the women included in the sample introducing uncertainty about the applicability of the results to the UK population. Most studies used an enzyme linked immunoassay (ELISA) to identify HSV, however the treatment of indeterminate results varied and no studies carried out confirmation tests on all samples using Western blot which is considered the gold standard reference standard. This introduces the possibility of false positive or false negative results.

Summary of Findings Relevant to Criteria 1: Criteria not met

Two questions were considered for this criterion, relating to UK incidence of neonatal herpes and UK seroprevalence of HSV-1 and HSV-2 in pregnant women.

The 2006 UK NSC review cited a UK prevalence of neonatal herpes of 4 per 100,000 live births based on cases identified in 2004-2005. This was an increase from a prevalence of 1.65 per 100,000 live births from 1986 to 1991. A more recent UK study identified for this review cited an incidence of neonatal herpes of 17.5 per 100,000 live births (95%CI 8.4 to 32.1). This was based on cases identified between 2006 and 2012 in a geographically defined, predominantly urban population. Due to a lack of detail about the study population it is not clear if the higher incidence in this population would apply to the UK as a whole.

The 2006 UK NSC evidence review referenced a study reporting seroprevalence for a general UK population of women. This gave an HSV-1 seroprevalence of 54% and an HSV-2 seroprevalence of 5.1%. This update review did not identify any studies reporting the seroprevalence of HSV-1 and HSV-2 in UK pregnant women. The seroprevalence of HSV-1 and HSV-2 in pregnant women in countries considered analogous to the UK varied considerably, ranging from 45% to 91% for HSV-1 and 9% to 22% for HSV-2. The applicability of these results to the UK is not clear.

In the absence of recent evidence about the UK seroprevalence of HSV in pregnant women and uncertainty about the incidence of neonatal herpes for the UK as a whole, this criterion is not met.

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

Question 3 – What is the accuracy of serologic screening for HSV-1 and HSV-2 in pregnancy?

The 2006 review described serological tests for HSV-2 as being relatively accurate but discussed the likelihood of false positive tests[3]. Details of test performance were not reported.

Eligibility for inclusion in the review

The inclusion criteria for this question are summarised briefly below:

- population – general pregnant population
- intervention – type specific serologic testing for HSV-1 and HSV-2. Type specific or combined testing
- comparator – western blot
- outcomes – measures of clinical validity of screening test (eg sensitivity; specificity; positive predictive value (PPV); negative predictive value (NPV)
- studies - studies in randomly assigned or consecutively enrolled populations and systematic reviews of these should be prioritised.

Description of the evidence

Database searches yielded 105 results, of which 27 were judged to be relevant to this question and 7 abstracts met the criteria for full text review. After review of the full texts, 1 study was included.

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

- 2 case control studies
- 1 study about willingness to be tested
- 1 study about the accuracy of tests in women with genital lesions
- 1 study comparing 2 screening tests with each other using laboratory samples, with no reference standard used
- 1 narrative 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.

No studies assessing the accuracy of serologic screening for HSV-1 in pregnant women met the criteria for inclusion. The recently updated USPSTF recommendation[7] noted that although serologic tests can identify HSV-1, they cannot distinguish between an oral or genital site of infection and are therefore not useful for screening asymptomatic adults for genital herpes.

One study (Leyland et al 2009[15]) reported screening test performance for HSV-2 in 399 pregnant women enrolled from 3 clinical sites in the USA between November 2006 and March 2007. The overall seroprevalence of HSV-2 in this population was 30.6%. The performance of 2 screening tests singly and combined was assessed using Immunoblot as the reference standard. The results are summarised in Table 4 with further details available in the Appendix 3 tables.

Table 4. Summary of the results from Leyland et al (2009)[15].

Screening test	Sensitivity	Specificity	PPV	NPV
EA	94.9%	96.4%	91.7%	97.8%
ELISA	99.1%	98.6%	96.7%	99.6%
EA and ELISA combined	94.9%	99.3%	98.2%	97.9%

EA - Express Assay; ELISA - Enzyme linked immunoassay; NPV – negative predictive value; PPV - positive predictive value

The quality of Leyland et al was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) framework. The QUADAS-2 framework is used to assess the quality of primary test accuracy studies and includes 5 domains on patient selection, the index test, the reference standard, test strategy flow and timing and applicability. The study was at low risk of bias in 8 of the 13 areas assessed. The only area in which the study was potentially at high risk of bias was in the exclusion of 4 women from the analysis. This included 3 women with equivocal ELISA results and 1 woman without an Immunoblot result. The exclusion of women from the analysis introduces the possibility that positive cases were missed. In

3 areas the risk of bias was unclear. This included a lack of information about whether the index tests were interpreted without knowledge of the reference standard result and the use of Immunoblot rather than Western blot as the reference standard. The study authors acknowledged that Western blot is an accepted gold standard but described Immunoblot as having similar performance characteristics to Western blot. Further details on the QUADAS-2 scores are provided in the Appendix 3 tables.

The test performance scores reported by Leyland et al are high. However the overall seroprevalence of HSV-2 in this population was 30.6% which is higher than the range of seroprevalence values in western populations discussed in question 2. The prevalence of HSV-2 in the population tested will influence the test performance scores, particularly affecting positive predictive value (PPV). Lower positive predictive scores would be associated with a higher proportion of false positive tests. To demonstrate this, Table 5 applies the range of HSV-2 seroprevalence scores discussed in question 2 to the sensitivity and specificity scores reported by Leyland et al.

Table 5. Test performance by seroprevalence.

Seroprevalence of HSV-2	Screening test	Sensitivity	Specificity	PPV	NPV
5%[§]	EA	94.9%	96.4%	58.1%	99.7%
	ELISA	99.1%	98.6%	78.8%	100%
	EA and ELISA combined	94.9%	99.3%	87.7%	99.7%
9%[**]	EA	94.9%	96.4%	72.3%	99.5%
	ELISA	99.1%	98.6%	87.5%	99.9%
	EA and ELISA combined	94.9%	99.3%	93.1%	99.5%
22%[††]	EA	94.9%	96.4%	88.1%	98.5%
	ELISA	99.1%	98.6%	95.2%	99.7%
	EA and ELISA combined	94.9%	99.3%	97.5%	98.6%

EA - Express Assay; ELISA - Enzyme linked immunoassay; NPV – negative predictive value; PPV - positive predictive value

[§] In a UK general population aged 16-69 reported by the 2006 UK NSC review
[**] Lower end of the range reported from new, non-UK studies included in question 2
[††] Upper end of the range reported from new, non-UK studies included in question 2

No study providing a current seroprevalence for HSV-2 in pregnant women in the UK was identified in question 2. However, if the seroprevalence is low then screening would generate more false positive screening tests than would be found in populations with a higher seroprevalence. False positive tests can cause anxiety and lead to women undergoing additional unnecessary tests. Negative predictive vales remained high for all of the scenarios modelled suggesting that a low proportion of false negatives would be expected, reducing the chance that women with HSV-2 would be missed.

Summary of Findings Relevant to Criteria 4: Criterion not met

The 2006 review described serological tests for HSV-2 as being relatively accurate but did not report specific figures. The likelihood of false positive tests was discussed.

The current review identified a study assessing the performance of screening tests for HSV-2 in a population of pregnant women. The sensitivity and specificity scores reported were high (over 90%). However, the seroprevalence was higher in this study (30.6%) than might be expected in the UK given the range of seroprevalence scores discussed in question 2 (5% to 22%). This suggests that lower positive predictive values might be expected in a UK pregnant population, leading to a higher proportion of false positive tests in the screened population.

No studies assessing the accuracy of serologic screening for HSV-1 in pregnant women met the criteria for inclusion.

In the absence of information about the accuracy of screening tests for HSV-1 in pregnant women and the uncertainties around test performance for HSV-2 in a UK pregnant population, this criterion 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 – Is there an effective management strategy to reduce the risk of HSV acquisition in seronegative pregnant women?

The 2006 UK NSC evidence review discussed management strategies, stating that seronegative women could be offered advice about potential ways to reduce their risk of acquiring the virus such as using a condom or only having intercourse with partners known to be free of infection. The 2006 review also stated that there was no evidence about whether this is likely to be an effective approach to prevention[3].

Eligibility for inclusion in the review

The inclusion criteria for this question are summarised briefly below:

- population – HSV seronegative pregnant women
- intervention – information and/or other interventions to prevent infection
- comparator – no intervention or placebo
- outcomes – reduced maternal HSV infection and reduced neonatal infection
- studies - RCTs, controlled clinical trials, observational studies with a comparison group and systematic reviews of these.

Description of the evidence

Database searches yielded 105 results, of which 10 were judged to be relevant to this question and 5 abstracts met the criteria for full text review. After review of the full texts, 1 study was included.

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

- 1 study about the risk of spontaneous abortion in women who became pregnant during a vaccine trial
- 1 study about symptoms and risk factors not management strategies
- 1 study about whether HSV is transmitted not management strategies to reduce risk
- 1 study about the willingness of partners of pregnant women to be tested for HSV.

Summary of findings

A study-level summary of data extracted from each included publication is presented in Appendix 3.

Delaney et al (2012)[16] assessed adherence to safer-sex practices in seronegative women according to their risk of acquiring HSV from their partners. This study included 287 pregnant women who had tested negative for HSV-2 during routine prenatal care. All women were offered free serologic testing for HSV-1 and HSV-2 for their sex partners and 193 partners were tested. All women also received counselling on safer-sex practices to prevent the acquisition of genital herpes during pregnancy. Women were divided into 4 groups‡‡ for analysis based on their risk of acquiring HSV-1 and/or HSV-2 from their partners. Outcomes were assessed from daily diaries of sexual activity and sexual behaviour questionnaires completed 1-2 times before delivery and once immediately after delivery. The median number of days of observation was 82 (range 30 to 235). Delaney et al found that women at risk of acquiring HSV-2 had a significantly lower rate of unprotected genital sex compared to women who were not at risk (relative risk (RR) 0.3 95%CI 0.1 to 0.8) or women of unknown risk (RR 0.2 95%CI 0.1 to 0.8). Women at risk of HSV-2 were also more likely to always use a condom (40%) compared to women not at risk (6%) and women of unknown risk (4%) (p=0.005). However there was no difference in rate of unprotected genital sex or rates of giving or receiving oral sex for women at risk of HSV-1 compared to women not at risk or women of unknown risk.

This study was assessed using the CASP cohort study checklist. This was a small study (n=287) and level of participation in follow-up was used

‡‡ The women were: at risk of acquiring HSV-1 from their partners; at risk of acquiring HSV-2 from their partners; of unknown risk; or not at risk

as an exclusion criteria. The results therefore represent the behaviour of women who were more motivated to participate in the study rather than the whole study population. The results were based on self-reported sexual activity and behaviour. Knowing that they were at risk of acquiring HSV through knowledge of the HSV status of their partner appears to have reduced risky behaviours for women at risk of HSV-2 but not HSV-1. This study does not provide any information on whether HSV-1 or HSV-2 was acquired by any of the women in the study or their neonates.

Question 5 – Is there an effective intervention for reducing vertical transmission of HSV from mother to child?

The 2006 review reported that the risk of neonatal infection has been associated with long duration of rupture of the membranes and the use of invasive obstetrical procedures such as fetal scalp electrodes[3]. The 2006 review also discussed the potential for offering antiviral therapy to seropositive women to reduce HSV shedding or the use of elective Caesarean section to reduce the risk of transmission. However, there was considered to be limited evidence for the effectiveness of these strategies[3].

Eligibility for inclusion in the review

The inclusion criteria for this question are summarised briefly below:

- population – pregnant women with HSV infection; seropositive pregnant women
- intervention – any intervention eg antiviral drugs, Caesarean section
- comparator – normal care
- outcomes – infection free newborn; reduction in sequelae
- studies – RCTs, controlled clinical trials, observational studies with a comparison group and systematic reviews of these. Studies in screen detected women should be prioritised.

Description of the evidence

Database searches yielded 105 results, of which 26 were judged to be relevant to this question and 12 abstracts met the criteria for full text review. After review of the full texts, 2 studies were included.

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

- 2 studies that were included in the systematic review
- 2 studies about risk factors for transmission
- 2 case series with no comparator
- 1 study about the effect of treatment for perinatal intrauterine herpes infection on preventing brain injury in preterm infants
- 1 retrospective review on the association between untreated herpes and pre-term delivery
- 1 retrospective review about the effect of knowledge of HSV-2 status on the management of positive women
- 1 retrospective review of the outcomes of women who tested positive for HSV-2.

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.

One systematic review (Hollier & Wendel 2008[17]) and 1 subsequently published randomised controlled trial (RCT) (Nakubulwa et al 2017[18]) were included.

Hollier & Wendel (2008[17]) included 7 RCTs assessing the effectiveness of antenatal antiviral prophylaxis in their systematic review. These RCTs included women in the third trimester who were diagnosed with genital herpes infection before or during pregnancy. In all studies, prophylaxis treatment started from 36 weeks. As no cases of symptomatic neonatal herpes were found in either the intervention or control groups in any of the 7 included studies, the systematic review authors were unable to draw any conclusions about the impact of antiviral prophylaxis on neonatal herpes. However, meta-analysis of the results for pregnant women did show reduced recurrence of genital herpes and less HSV detected at delivery for the intervention group. The use of antiviral prophylaxis was also associated with fewer Caesarean deliveries. Overall, the authors calculated that the number of women who would need to receive antiviral prophylaxis from 36 weeks until delivery was:

- 10 to prevent a recurrence of genital herpes at delivery
- 17 to prevent HSV detection at delivery
- 10 to prevent a Caesarean delivery.

This study was assessed using the CASP systematic review checklist. There were no areas of concern in the design or reporting of the review. However, it was notable that the included RCTs were small and that 3 were terminated early due to slow enrolment. The review authors' assessment of the included studies according to Cochrane guidelines identified a few areas of uncertainty (eg around blinding and randomisation), but generally did not identify any serious concerns.

Nakubulwa et al (2017[18]) conducted a double-blind RCT comparing antiviral prophylaxis to placebo in 200 HSV-2 positive pregnant women screened between 20 and 26 weeks gestation. The objective of this study was to determine the effect of oral antiviral prophylaxis administered from 28 to 36 weeks gestation on obstetric outcomes. All women in the study afterwards received prophylaxis from 36 weeks onwards. There was no significant difference in the incidence of premature rupture of membranes between the intervention and placebo group by 36 weeks. There was also no significant difference between the 2 groups in HSV-2 shedding at birth or low birth rate. The study did find a significant reduction in the incidence of preterm delivery (<37 weeks) for the intervention group (11% vs 24%; RR 0.41 95%CI 0.20 to 0.85, p=0.016) and in admissions to the special care unit (9% vs 17%; RR 0.43 95%CI 0.19 to 0.96, p=0.040). The study did not report neonatal infection.

The study was assessed using the Cochrane Collaboration's tool for assessing risk of bias in RCTs. There were no concerns relating to the selection, randomisation or blinding of participants and researchers or the reporting of results. An intention to treat analysis was performed. There were some issues in compliance with the study medication schedule with only about half of the participants fully complying in both groups. This was a small study (n=200) set in Uganda in a population with an HSV-2 prevalence of over 60.0% in pregnant women which is likely to be higher than would be found in the UK. This may limit the applicability of the results to a UK context.

Summary of Findings Relevant to Criterion 9: Criterion not met

Two questions were considered for this criterion, relating to the management of seronegative pregnant women and interventions for reducing vertical transmission from mother to child.

The 2006 UK NSC evidence review discussed management strategies, stating that seronegative women could be offered advice about potential ways to reduce their risk of acquiring HSV but did not find any evidence about whether such strategies would be effective. A small study identified for the current review suggests that knowing that they are at risk of acquiring HSV through knowledge of their sex partner's HSV status may reduce risky behaviours in women at risk of HSV-2 but not HSV-1.A reduction in risky behaviours should reduce the risk of HSV acquisition in seronegative women, however this particular study does not provide information about whether HSV was acquired or not acquired by these women or their neonates.

The 2006 review reported associations between the risk of neonatal infection and long duration of rupture of the membranes and the use of invasive obstetrical procedures such as fetal scalp electrodes and discussed the potential for offering antiviral therapy to seropositive women to reduce HSV shedding or the use of elective Caesarean section to reduce the risk of transmission. However, there was considered to be limited evidence for the effectiveness of these strategies.

The current review identified some evidence for the effectiveness of oral antiviral therapy in reducing recurrence of genital herpes and reduction in HSV shedding at birth. There was also some evidence that oral antiviral therapy may reduce the number of elective Caesarean sections that are performed and reduce the incidence of pre-term delivery. However these studies do not provide any evidence about the whether these reductions translate into fewer cases of vertical transmission of HSV from mother to child.

Studies were identified suggesting that intervention can reduce risky behaviours in seronegative women or reduce risk factors for vertical transmission in women with HSV infection. However these were small studies which did not establish whether intervention reduces neonatal infection. Therefore this criterion is not met.

Review summary

Conclusions and implications for policy

This report is an update review on systematic antenatal screening for HSV-1 and HSV-2 infection to prevent neonatal herpes infection 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 2005 suggests that reconsideration of the current recommendation for screening for HSV-1 and HSV-2 in the UK is required.

The volume, quality and direction of new evidence published since October 2005 does not indicate that there have been any significant changes in the evidence base since the previous review. Key areas of concern relate to:

- there are uncertainties about the seroprevalence of HSV-1 and HSV-2 in UK pregnant women
- there is an absence of evidence about the performance of screening tests for HSV-1 in pregnant women
- there are uncertainties about the performance of screening tests for HSV-2 in UK pregnant women, particularly around the number of false positive tests that might be expected
- there is some evidence that intervention (eg knowledge of a sex partner's HSV status) can reduce risky behaviours in women seronegative for HSV-2. There is also some evidence that intervention (eg oral antiviral therapy) can reduce risk factors for vertical transmission for women with HSV infection. However the resulting impact on neonatal infection was not established.

The current recommendation not to introduce a UK systematic antenatal population screening programme for HSV-1 and HSV-2 infection should be retained.

Limitations

A limitation for this review is the lack of evidence specific to pregnant women, particularly around the UK prevalence of HSV and performance of screening tests for HSV-1.

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	2005 to Present
Embase	Ovid SP	21st February 2018	2005 to Present
The Cochrane Library	Wiley Online	21st February 2018	2005 to Present

Search Terms

Search terms for MEDLINE are shown in Table 7 for each of the 5 review questions. A similar search was conducted in 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 Herpes Simplex/	23175
2	simplexvirus/ or herpesvirus 1, human/ or herpesvirus 2, human/	28717
3	herpes*.ti.	45661
4	(herpessimplex or herpes simplex or (genital* adj2 herpes*)).ti,ab.	39591
5	("herpes virus 1" or "herpesvirus1" or "herpes virus i" or "herpesvirus i" or "herpes virus 2" or "herpesvirus2" or "herpes virus ii" or "herpesvirus ii").ti,ab.	342
6	("hsv 1" or "hsv i" or HSV-1 or "hsv 2" or "hsv ii" or HSV-2).ti,ab.	15259
7	1 or 2 or 3 or 4 or 5 or 6	71026
8	infant/ or exp infant, newborn/	1055520
9	(neonat* or infant* or baby or babies or newborn?).ti,ab.	636074
10	8 or 9	1309259
11	7 and 10	5701
12	((neonat* or infant* or baby or babies or newborn?) adj5 (herpes* or hsv*)).ti,ab.	1390
13	11 or 12	5742
14	INCIDENCE/	225972
15	Registries/	72494
16	(incidence or cases).ti,ab. or epidemiolog*.ti.	2288421
17	(register? or registry or registries or (national adj3 data)).ti,ab.	173568
18	14 or 15 or 16 or 17	2499226
19	13 and 18	1438
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	116
24	limit 23 to (english language and yr="2005 -Current")	62
25	(case reports or comment or editorial or letter or news or "review").pt.	5647694
26	24 not 25	44
27	limit 19 to "reviews (maximizes specificity)"	12
28	limit 27 to (english language and yr="2005 -Current")	10
29	26 or 28	71
Question 2		
1	exp Herpes Simplex/	23175
2	simplexvirus/ or herpesvirus 1, human/ or herpesvirus 2, human/	28717
3	herpes*.ti.	45661
4	(herpessimplex or herpes simplex or (genital* adj2 herpes*)).ti,ab.	39591
5	("herpes virus 1" or "herpesvirus1" or "herpes virus i" or "herpesvirus i" or "herpes virus 2" or "herpesvirus2" or "herpes virus ii" or "herpesvirus ii").ti,ab.	342
6	("hsv 1" or "hsv i" or HSV-1 or "hsv 2" or "hsv ii" or HSV-2).ti,ab.	15259
7	1 or 2 or 3 or 4 or 5 or 6	71026
8	Pregnant Women/	6510
9	Pregnancy/	810647
10	preconception care/ or prenatal care/	25261
11	Maternal Health/	606
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*).ti,ab.	723551
13	8 or 9 or 10 or 11 or 12	1094065
14	7 and 13	3745
15	((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 (herpes* or hsv*)).ti,ab.	916
16	14 or 15	3798
17	prevalence/	247010
18	Cross-Sectional Studies/	257115
19	(prevalence or seroprevalence or sero-prevalence).ti,ab. or epidemiolog*.ti.	616373
20	(crosssectional or cross-sectional).ti,ab.	269405
21	exp Herpes Simplex/ep [Epidemiology]	2039
22	17 or 18 or 19 or 20 or 21	966570
23	16 and 22	768
24	exp United Kingdom/	341134
25	(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
26	24 or 25	1642177
27	23 and 26	93
28	limit 27 to (english language and yr="2005 -Current")	49
29	(case reports or comment or editorial or letter or news or "review").pt.	5647694
30	28 not 29	43
31	limit 23 to (english language and yr="2005 -Current" and "reviews (maximizes specificity)")	7

32	30 or 31	49
Question 3		
1	exp Herpes Simplex/	23175
2	simplexvirus/ or herpesvirus 1, human/ or herpesvirus 2, human/	28717
3	herpes*.ti.	45661
4	(herpessimplex or herpes simplex or (genital* adj2 herpes*)).ti,ab.	39591
5	("herpes virus 1" or "herpesvirus1" or "herpes virus i" or "herpesvirus i" or "herpes virus 2" or "herpesvirus2" or "herpes virus ii" or "herpesvirus ii").ti,ab.	342
6	("hsv 1" or "hsv i" or HSV-1 or "hsv 2" or "hsv ii" or HSV-2).ti,ab.	15259
7	1 or 2 or 3 or 4 or 5 or 6	71026
8	Pregnant Women/	6510
9	Pregnancy/	810647
10	preconception care/ or prenatal care/	25261
11	Maternal Health/	606
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*).ti,ab.	723551
13	8 or 9 or 10 or 11 or 12	1094065
14	7 and 13	3745
15	((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 (herpes* or hsv*)).ti,ab.	916
16	14 or 15	3798
17	prenatal diagnosis/ or maternal serum screening tests/	34734
18	Diagnostic Tests, Routine/	9737
19	Serologic Tests/	18837
20	((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 (test* or screen* or diagnos*)).ti,ab.	75859
21	(routine adj5 (test* or screen* or diagnos*)).ti,ab.	41457
22	((sero* adj5 (test* or screen* or diagnos*)) or (serotest* or seroscreen* or serodiagnos*)).ti,ab.	47281
23	((herpes* or hsv*) adj5 (test* or screen* or diagnos*)).ti,ab.	4577
24	(test* or screen* or diagnos*).ti.	1020568
25	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	1146719
26	16 and 25	813
27	limit 26 to (english language and yr="2005 -Current")	302
28	(case reports or comment or editorial or letter or news or "review").pt.	5647694
29	27 not 28	212
30	limit 26 to "reviews (maximizes specificity)"	14
31	limit 30 to (english language and yr="2005 -Current")	9
32	29 or 31	220
Question 4		
1	exp Herpes Simplex/	23175
2	simplexvirus/ or herpesvirus 1, human/ or herpesvirus 2, human/	28717
3	herpes*.ti.	45661
4	(herpessimplex or herpes simplex or (genital* adj2 herpes*)).ti,ab.	39591
5	("herpes virus 1" or "herpesvirus1" or "herpes virus i" or "herpesvirus i" or "herpes virus 2" or "herpesvirus2" or "herpes	342

	virus ii" or "herpesvirus ii").ti,ab.	
6	("hsv 1" or "hsv i" or HSV-1 or "hsv 2" or "hsv ii" or HSV-2).ti,ab.	15259
7	1 or 2 or 3 or 4 or 5 or 6	71026
8	Pregnant Women/	6510
9	Pregnancy/	810647
10	preconception care/ or prenatal care/	25261
11	Maternal Health/	606
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*).ti,ab.	723551
13	8 or 9 or 10 or 11 or 12	1094065
14	7 and 13	3745
15	((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 (herpes* or hsv*)).ti,ab.	916
16	14 or 15	3798
17	exp preventive health services/	535864
18	safe sex/ or sexual abstinence/	3987
19	exp Herpes Simplex/pc	2011
20	(health adj5 (educat* or promot*)).ti,ab.	104819
21	((herpes* or hsv*) adj5 (educat* or promot*)).ti,ab.	1217
22	((herpes* or hsv*) adj5 (prevent* or prophyla*)).ti,ab.	1618
23	(prevent* or prophyla*).ti.	304846
24	(sex* adj5 (abstinen* or abstain* or restrain* or refrain*)).ti,ab.	1541
25	(seronegative or sero-negative or seroconver* or sero-conver*).ti,ab.	32604
26	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	897305
27	16 and 26	753
28	limit 27 to (english language and yr="2005 -Current")	260
29	(case reports or comment or editorial or letter or news or "review").pt.	5647694
30	28 not 29	181
31	limit 27 to (english language and yr="2005 -Current" and "reviews (maximizes specificity)")	16
32	30 or 31	191
Question 5		
1	exp Herpes Simplex/	23175
2	simplexvirus/ or herpesvirus 1, human/ or herpesvirus 2, human/	28717
3	herpes*.ti.	45661
4	(herpessimplex or herpes simplex or (genital* adj2 herpes*)).ti,ab.	39591
5	("herpes virus 1" or "herpesvirus1" or "herpes virus i" or "herpesvirus i" or "herpes virus 2" or "herpesvirus2" or "herpes virus ii" or "herpesvirus ii").ti,ab.	342
6	("hsv 1" or "hsv i" or HSV-1 or "hsv 2" or "hsv ii" or HSV-2).ti,ab.	15259
7	1 or 2 or 3 or 4 or 5 or 6	71026
8	Pregnant Women/	6510
9	Pregnancy/	810647
10	preconception care/ or prenatal care/	25261
11	Maternal Health/	606
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*).ti,ab.	723551
13	8 or 9 or 10 or 11 or 12	1094065

14	7 and 13	3745
15	((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 (herpes* or hsv*)).ti,ab.	916
16	14 or 15	3798
17	infectious disease transmission, vertical/	14093
18	exp Delivery, Obstetric/ and disease transmission, infectious/	5
19	((mother? or maternal) adj2 (neonat* or infant? or child? or f?etal or f?etus) adj5 transmi*).ti,ab.	6703
20	(vertical adj5 transmi*).ti,ab.	6252
21	17 or 18 or 19 or 20	20277
22	7 and 21	501
23	exp Herpes Simplex/tm	1096
24	transmi*.ti.	84527
25	23 or 24	85403
26	16 and 25	632
27	22 or 26	908
28	limit 27 to (english language and yr="2005 -Current")	305
29	(case reports or comment or editorial or letter or news or "review").pt.	5647694
30	28 not 29	175
31	limit 27 to (english language and "reviews (maximizes specificity)" and yr="2005 -Current")	11
32	30 or 31	182

Table 8. Search strategy for the Cochrane Library Databases.

#	Search terms
#1	MeSH descriptor: [Herpes Simplex] explode all trees
#2	MeSH descriptor: [Herpesvirus 1, Human] explode all trees
#3	MeSH descriptor: [Herpesvirus 2, Human] explode all trees
#4	herpes*:ti (Word variations have been searched)
#5	(herpessimplex or herpes simplex or (genital* near/2 herpes*)):ti,ab,kw (Word variations have been searched)
#6	herpes virus 1 or "herpesvirus1" or "herpes virus i" or "herpesvirus i" or "herpes virus 2" or "herpesvirus2" or "herpes virus ii" or "herpesvirus ii":ti,ab,kw (Word variations have been searched)
#7	hsv 1 or "hsv i" or hsv1 or "hsv 2" or "hsv ii" or hsv2:ti,ab,kw (Word variations have been searched)
#8	#1 or #2 or #3 or #4 or #5 or #6 or #7
#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,kw (Word variations have been searched)
#10	#8 and #9
#11	neonat* or newborn* or infan* or baby or babies:ti,ab,kw (Word variations have been searched)
#12	#8 and #11

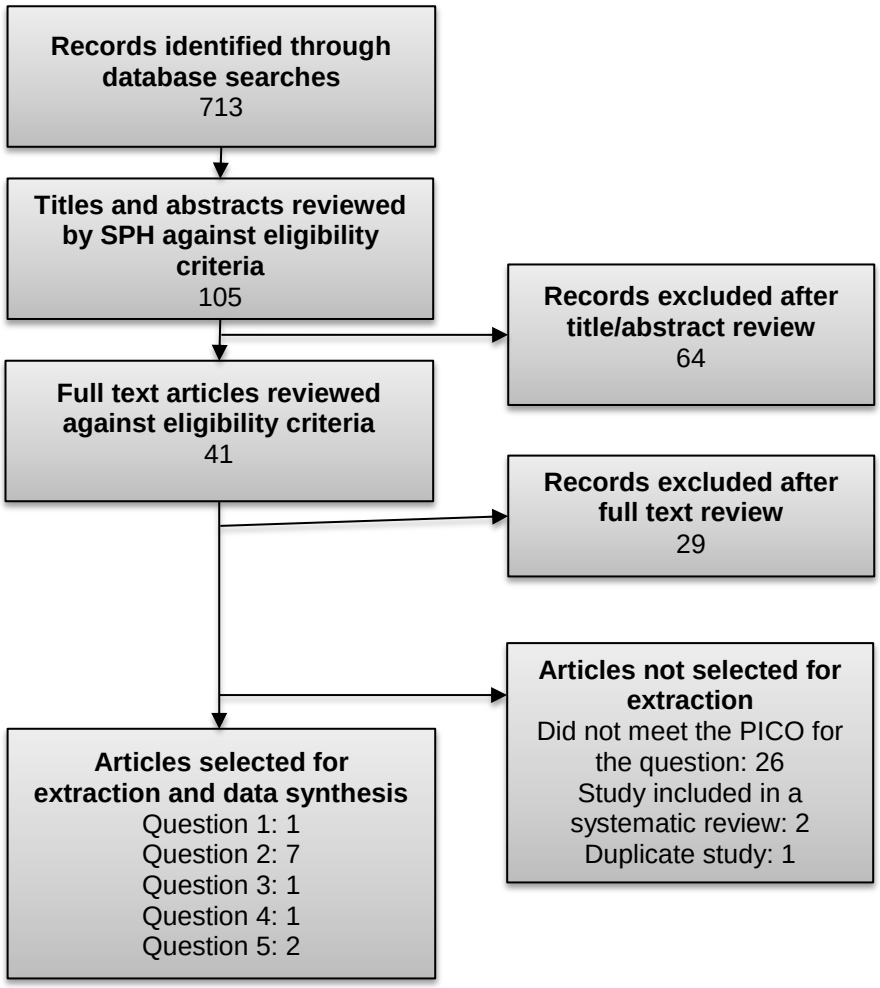
Duplicate references were removed.

Appendix 2 — Included and excluded studies

PRISMA flowchart

Figure 1 summarises the volume of publications included and excluded at each stage of the review. 105 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 1. Summary of publications included and excluded at each stage of the review.



Publications included after review of full text articles

The 12 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. In question 5, 2 individual studies that were included in a systematic review identified were not considered separately.

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
Batra et al (2014)[4]	x			
Marchi et al (2017)[8]	x			
Puhakka et al (2016)[9]	x			
Kucera et al (2012)[10]	x			
Sauerbrei et al (2011)[11]	x			
Berntsson et al (2009)[12]	x			
Sasadeusz et al (2009)[13]	x			
Xu et al (2007)[14]	x			
Leyland et al (2009)[15]		x		
Delaney et al (2012)[16]			x	
Hollier & Wendel 2008[17]			x	
Nakubulwa et al 2017[18]			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 incidence of neonatal herpes in the UK?

Table 10. Batra et al (2014)[4]

Publication	Batra D. Davies P. Manktelow BN. Smith C. The incidence and presentation of neonatal herpes in a single UK tertiary centre, 2006-2013. Arch. Dis. Child 2014, 99: 916-921
Study details	Cohort study reviewing neonatal herpes infection cases at 1 UK centre
Study objectives	To determine the incidence of neonatal herpes in the UK and describe the presentation of neonatal cases
Inclusions	All patients up to 28 days old with a positive test for HSV born between January 2006 and December 2013
Exclusions	None stated
Population	A study area was defined, based on mother's postcode in order to estimate the incidence of neonatal herpes in a geographically defined population. This calculation used the total number of live births between 2006 and 2012 as 2013 data was not available The presentation of neonatal herpes was described for 19 patients born at or treated at the centre The study population came from a predominantly urban population. The precise location was not specified
Intervention	N/a
Comparator	N/a
Outcomes	**Incidence of neonatal herpes** There were 10 cases of neonatal herpes from 57,291 live births, equating to an incidence of 17.5 per 100,000 live births (95%CI 8.4 to 32.1) **Presentation of neonatal herpes cases** 19 patients with neonatal herpes were born at or treated at the centre: • 9 HSV-1 cases • 8 HSV-2 cases • 2 cases of unknown serotype 4 cases presented within 48 hours of birth and represented either in utero or early perinatal infection. The other cases presented between 3 and 14 days after birth
Quality appraisal	The study was assessed using the JBI critical appraisal checklist for studies reporting prevalence data. There were a small number of cases over the 6 year timeframe with wide confidence intervals around the incidence figure. There were limited details about the geographical location of the study within the UK.

Key question 2: What is the seroprevalence of HSV-1 and HSV-2 in pregnant women in the UK?

Table 11. Marchi et al (2017)[8]

Publication	Marchi S. Trombetta CM. Gasparini R. Temperton N. Montomoli E. Epidemiology of herpes simplex virus type 1 and 2 in Italy: a seroprevalence study from 2000 to 2014. J. Prev Med. Hyg. 2017, 58: E27-E33
Study details	Cohort study assessing HSV-1 and HSV-2 seroprevalence in Italy
Study objectives	To assess HSV-1 and HSV-2 seroprevalence in pregnant women in 1 Italian region
Inclusions	None stated
Exclusions	None stated
Population	Serum samples were taken from a serum bank at an Italian university. This included 91 samples from pregnant women from the Bari area of Italy, collected in 2003, 2004 and 2005
Intervention	N/a
Comparator	N/a
Outcomes	ELISA was used to test for HSV-1 and HSV-2 83 pregnant women tested positive for HSV-1 antibodies equating to a seroprevalence of 91.2% (confidence intervals not reported) 9 pregnant women tested positive for HSV-2 antibodies equating to a seroprevalence of 9.9% (confidence intervals not reported)
Quality appraisal	The study was assessed using the JBI critical appraisal checklist for studies reporting prevalence data. The study sample size was very small and no demographic details were provided about the pregnant women. Samples were taken from a serum bank and it is not clear how women were selected for inclusion. Borderline results were excluded from the analysis suggesting that positive samples could have been missed. There is no indication that test results were confirmed using the gold standard Western blot test introducing the possibility of false positive or false negative tests.

Table 12. Puhakka et al (2016)[9]

Publication	Puhakka L. Sarvikivi E. Lappalainen M. Surcel HM. Saxen H. Decrease in seroprevalence for herpesviruses among pregnant women in Finland: cross-sectional study of three time points 1992, 2002 and 2012. Infectious Diseases 2016, 48 (5): 406-410
Study details	Cohort study assessing HSV-1 and HSV-2 seroprevalence in Finland using samples from a national database
Study objectives	To assess HSV-1 and HSV-2 seroprevalence in pregnant women in Finland
Inclusions	Samples from a Finnish database
Exclusions	None stated
Population	600 samples were randomly taken from a Finnish national biorepository containing serum samples from almost all pregnant Finnish women since 1983. Samples from 3 time points were tested (200 samples per year for 1992, 2002 and 2012). Samples were taken during the first and early second trimesters of pregnancy
Intervention	N/a
Comparator	N/a
Outcomes	ELISA was used to test for HSV-1 and HSV-2. No borderline results were

	reported The seroprevalence of HSV-1 antibodies decreased from 69.5% (95%CI 62.6 to 75.8) in 1992 to 45.0% (95%CI 38.0 to 52.2) in 2012 The seroprevalence of HSV-2 antibodies decreased from 17.5% (95%CI 12.5 to 23.5) in 1992 to 11% (95%CI 7.0 to 16.2) in 2012 Data for 2002 was only reported graphically and is not reproduced here
Quality appraisal	The study was assessed using the JBI critical appraisal checklist for studies reporting prevalence data. The sample size was small. Samples were taken from a national database of stored samples from pregnant women. No demographic details were provided about the women that the samples came from. There is no indication that test results were confirmed using the gold standard Western blot test introducing the possibility of false positive or false negative tests.

Table 13. Kucera et al (2012)[10]

Publication	Kucera P. Gerber S. Marques-Vidal P. Meylan PRA. Seroepidemiology of herpes simplex virus type 1 and 2 in pregnant women in Switzerland: an obstetric clinic based study. European Journal of Obstetrics & Gynecology and Reproductive Biology 2012, 160: 13-17
Study details	Cohort study assessing HSV-1 and HSV-2 seroprevalence in 1 Swiss centre
Study objectives	To assess HSV-1 and HSV-2 seroprevalence in pregnant women in Switzerland
Inclusions	Able to give informed consent in French, German or English Attended the clinic for their early pregnancy visit
Exclusions	None stated
Population	1,030 women attending an antenatal clinic in Lausanne during their first trimester between December 2004 and September 2007. 64% of the study population were of European origin, 17% African, 5% Indian and 4% Asian
Intervention	N/a
Comparator	N/a
Outcomes	ELISA was used to test for HSV-1 and HSV-2. Samples with indeterminate results were rerun. Generic HSV tests that do not distinguish between HSV-1 and HSV-2 were performed in patients with persistently indeterminate results 818 women tested positive for HSV-1 antibodies, equating to a seroprevalence of 79.4% (95%CI 76.9 to 81.9) 218 women tested positive for HSV-2 antibodies, equating to a seroprevalence of 21.2% (95%CI 18.7 to 23.7)
Quality appraisal	The study was assessed using the JBI critical appraisal checklist for studies reporting prevalence data. The sample size was small. The authors indicated that barriers to recruiting women for the study included the fact that two-thirds of the delivering mothers at the clinic received their early pregnancy care privately and were therefore not eligible to participate and about one-third of attending women could not be asked to consent due to language barriers. The authors also stated that there were periods of work overload when midwives could not request consent to participate in the study due to time constraints. 1,030 of the 1,300 women of whom informed consent could be requested agreed to participate. This introduces a potential source of bias in the sample of women from this clinic who were tested. There is no indication that test results were confirmed using the gold standard Western blot test introducing the possibility of false positive or false negative tests.

Table 14. Sauerbrei et al (2011)[11]

Publication	Sauerbrei A. Schmitt S. Scheper T. et al. Seroprevalence of herpes simplex virus type 1 and type 2 in Thuringia Germany, 1999 to 2006. Euro Surveill. 2011, 16(44): pii=20005
Study details	Cohort study assessing HSV-1 and HSV-2 seroprevalence in 1 German centre
Study objectives	To assess HSV-1 and HSV-2 seroprevalence in pregnant women in Germany
Inclusions	None stated
Exclusions	None stated
Population	200 consecutively enrolled pregnant women who delivered at their local district hospital in Thuringia, Germany between January 1999 and January 2000
Intervention	N/a
Comparator	N/a
Outcomes	ELISA was used to test for HSV-1 and HSV-2. Indeterminate results were retested twice. Equivocal results after retesting were assessed using immunoblot. Positive ELISA tests were also analysed using immunoblot to avoid false positive results 164 pregnant women tested positive for HSV-1 antibodies equating to a seroprevalence of 82.0% (95%CI 76.0 to 87.1) 36 pregnant women tested positive for HSV-2 antibodies equating to a seroprevalence of 18.0% (95%CI 12.9 to 24.0)
Quality appraisal	The study was assessed using the JBI critical appraisal checklist for studies reporting prevalence data. The sample size was small and no demographic details were provided about the pregnant women. Equivocal and positive samples received immunoblot conformation testing. This was not performed for samples that were negative on ELISA introducing the possibility of false negatives. Women were described as being consecutively enrolled over a 12 month period but no details on response rate or total eligible population are provided.

Table 15. Berntsson et al (2009)[12]

Publication	Berntsson M. Tunbäck P. Ellström A. Krantz I. Löwhagen GB. Decreasing prevalence of herpes simplex virus-2 antibodies in selected groups of women in Sweden. Acta Derm. Venerol 2009, 89: 623-626
Study details	Cohort study assessing HSV-2 seroprevalence in 1 Swedish clinic
Study objectives	To assess HSV-2 seroprevalence in pregnant women in Sweden
Inclusions	None stated
Exclusions	None stated
Population	Testing for HSV-2 was conducted on 299 randomly selected samples taken from 661 consecutive attendees who had blood taken for routine HIV and rubella testing at an antenatal clinic in Gothenburg Sweden during 2002. The majority of women were in their first trimester
Intervention	N/a
Comparator	N/a
Outcomes	In-house and commercial ELISA kits were used to test for HSV-2 27 pregnant women tested positive for HSV-2 antibodies using the commercial ELISA test equating to a seroprevalence of 9.0% (95%CI 6.3 to 12.8) 31 pregnant women tested positive for HSV-2 antibodies using the in-house ELISA test equating to a seroprevalence of 10.4% (95%CI 7.4 to 14.3)
Quality	The study was assessed using the JBI critical appraisal checklist for studies

appraisal	reporting prevalence data. The study sample size was small and no demographic details were provided about the pregnant women. There is no indication that test results were confirmed using the gold standard Western blot test introducing the possibility of false positive or false negative tests. Samples were taken from a random sample of consecutively attendees at a clinic but no details on response rate or total eligible population are provided.

Table 16. Sasadeusz et al (2008)[13]

Publication	Sasadeusz JJ. Silvers JE. Kent HE. et al. Prevalence of HSV-2 antibody in a Melbourne antenatal population attending a tertiary obstetric hospital. Australian and New Zealand Journal of Obstetrics and Gynaecology 2008, 48: 266-272
Study details	Cohort study assessing HSV-2 seroprevalence in 1 Australian centre
Study objectives	To assess the seroprevalence of HSV-2 in pregnant women in Melbourne, Australia
Inclusions	Women able to speak English
Exclusions	None stated
Population	1,371 women attending an antenatal clinic in Melbourne between May 2000 and November 2002. 86% of women identified as Caucasian
Intervention	N/a
Comparator	N/a
Outcomes	ELISA was used to test for HSV-2. Samples considered indeterminate on ELISA (n=5) were further assessed with Western blot assay 187 women tested positive for HSV-2 antibodies, equating to a seroprevalence of 13.6% (95%CI 11.87 to 15.57)
Quality appraisal	The study was assessed using the JBI critical appraisal checklist for studies reporting prevalence data. The sample size for this study was small. 1,392 women initially consented to participate but 21 women were not included in the results. Reasons for non-evaluation included withdrawal of consent (n=7), insufficient sera available at recruitment (n=11) and non-completion of a questionnaire about their demographics and history (n=3). Only indeterminate samples were confirmed with Western blot which is considered the gold standard for confirming HSV introducing the possibility of false positive or false negative tests.

Table 17. Xu et al (2007)[14]

Publication	Xu F. Markowitz LE. Gottlieb SL. Berman SM. Seroprevalence of herpes simplex virus types 1 and 2 in pregnant women in the United States. Am. J. Obstet. Gynecol 2007, 196 (43): e1-43.e6
Study details	Cohort study assessing HSV-1 and HSV-2 seroprevalence in the US
Study objectives	To assess HSV-1 and HSV-2 seroprevalence in US pregnant women
Inclusions	Pregnant women aged 14 to 49 years old
Exclusions	None stated
Population	626 pregnant women who took part in a national Health and Nutrition Examination Survey between 1999 and 2002 and had HSV serology results available. 58% of the population was described as ‘white’; 15% as ‘black’ and 14% as Mexican American
Intervention	N/a
Comparator	N/a
Outcomes	Immunodot assays were used to test for HSV-1 and HSV-2 HSV-1 seroprevalence 63% (confidence intervals not reported)

	HSV-2 seroprevalence 22% (95%CI 16 to 31)
Quality appraisal	The study was assessed using the JBI critical appraisal checklist for studies reporting prevalence data. The study sample was small and recruited from women who participated in a national health survey. The study authors report that 83% of participants aged 14 to 49 who were originally selected for the survey were interviewed and 79% took part in a physical examination. The study authors report that of 704 pregnant women, 700 were aged between 14 and 49 and 626 had HSV serology results available. Reasons for missing HSV tests included refusal, unsuccessful venepuncture or the need to use the serum sample for other tests. There is no indication that test results were confirmed using the gold standard Western blot test introducing the possibility of false positive or false negative tests.

Data extraction and quality assessment for studies relevant to criterion 4

Key question 3: What is the accuracy of serologic screening for HSV-1 and HSV-2 in pregnancy?

Table 18. Leyland et al (2009)[15]

Publication	Leyland B. Kennedy MR. Wimberly YH. Levine BJ. Cherpes TL. Serologic detection of herpes simplex virus type 2 antibodies among pregnant women using a point-of-care test from Focus Diagnostics. J. Clin. Virol. 2009, 44(2): 125-128
Study details	Test performance study
Study objectives	To test the performance of a point-of-care test (Focus HerpeSelect® Express Assay) for the detection of HSV-2 antibodies in pregnant women
Inclusions	Pregnant women
Exclusions	None stated
Population	399 pregnant women from 3 US clinical sites (Atlanta, Georgia (n=160); Moorestown, New Jersey (n=102); Pittsburgh Pennsylvania (n=119))
Test	Express assay (EA) point of care test. An EA result was considered positive if the test strip coloured pink or red. An absence of colour along the test strip was considered a negative result Enzyme linked immunoassay (ELISA). An ELISA result >1.1 was considered positive, values from 0.9 to 1.1 were considered equivocal and, values <0.9 were considered negative. Equivocal ELISA tests were not retested
Comparator / reference standard	Immunoblot assays
Outcomes	Overall prevalence HSV-2: 30.6% The study authors reported test performance for EA and ELISA separately and combined using Immunoblot as the reference standard: **EA:** Sensitivity: 94.9% PPV: 91.7% Specificity: 96.4% NPV: 97.8% **ELISA:** Sensitivity: 99.1% PPV: 96.7% Specificity: 98.6% NPV: 99.6% **EA and ELISA combined:** Sensitivity: 94.9% PPV: 98.2% Specificity: 99.3% NPV: 97.9%

The study authors also reported EA test performance with ELISA as the reference standard using a cut-off of >1.1 for a positive result:
Sensitivity: 94.2% PPV: 93.4%
Specificity: 97.1% NPV: 97.4%

95% confidence intervals not reported

Quality appraisal using Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool			
Question	**Assessment (Y, N, unclear)**	**Risk of Bias (low, high, unclear)**	**Supporting info**
Domain I: Patient selection			
Consecutive or random sample of population enrolled?	Y	Low	Pregnant women enrolled from 3 clinical sites between November 2006 and March 2007
Case-control design avoided?	Y	Low	
Inappropriate exclusions avoided?	Y	Low	No exclusions stated
Domain II: Index Test			
Index test results interpreted without knowledge of reference standard results?	Unclear	Unclear	Not stated
Threshold pre-specified?	Y	Low	
Domain III: Reference standard			
Reference standard likely to correctly classify condition?	Unclear	Unclear	Western blot is considered the gold standard. Immunoblot is described by the study authors as having similar performance characteristics as Western blot for the serodiagnosis of HSV-2
Reference standard results interpreted without knowledge of index test results?	Y	Low	ELISA and immunoblot assays performed without knowledge of the EA result
Domain IV: Test strategy flow and timing			
Appropriate interval between index test and reference standard?	Y	Low	Tests performed from the serum samples taken at the same time
Did all participants receive same reference standard?	Y	Low	
All patients included in analysis?	N	High	4 women excluded; 3 with equivocal ELISA results and 1 for whom immunoblot results were unavailable
Domain V: Applicability			
Applicable to UK screening population of	Uncertain	Uncertain	High prevalence of HSV-2 in the study populations

interest?			
Applicable to UK screening test of interest?	Y	Low	Test available in the UK
Target condition measured by reference test applicable to UK screening condition of interest?	Unclear	Unclear	Western blot is considered the gold standard. Immunoblot is described by the study authors as having similar performance characteristics as Western blot for the serodiagnosis of HSV-2
Other comments			

Data extraction and quality assessment for studies relevant to criterion 9

Key question 4: Is there an effective management strategy to reduce the risk of HSV acquisition in seronegative pregnant women?

Table 19. Delaney et al (2012)[16]

Publication	Delaney S. Gardella C. Daruthayan C. et al. A prospective cohort study of partner testing for herpes simplex virus and sexual behaviour during pregnancy. JID 2012, 206: 486-494
Study details	Cohort study comparing behaviour in pregnant women by risk of HSV infection
Study objectives	To assess adherence to safer-sex practices in seronegative women at risk of HSV acquisition from their partners
Inclusions	• HSV-2 seronegative on Western blot testing • ≤31 weeks gestation • ≥18 years old • English speakers
Exclusions	Reasons for not including women who had initially agreed to participate in the study were: they did not have a partner; their partner was out of the country for the duration of the study; or they were told by their physician to abstain from sexual activity Only women who reported having ≥1 sexual partner during pregnancy and who were followed for at least 30 days were included in the analysis Women with <15 valid diary-days after they learned their partner's HSV status were excluded from the analysis
Population	287 pregnant women who were seronegative for HSV-2 during routine prenatal care at the University of Washington, USA between 2001 and 2008. 193 partners were tested
Intervention	All women were offered free serologic testing for HSV-1 and HSV-2 for their sex partners (at any time before delivery) All women were given standardised counselling on safer-sex practices to prevent the acquisition of genital herpes during pregnancy, including a booklet about HSV, a handout about HSV in pregnancy and a card describing safer-sex practices Women completed daily diaries of sexual activity and sexual behaviour questionnaires 1-2 times before delivery and once immediately after delivery

Comparator	N/a
Outcomes	Women and their partners were divided into 4 groups for the analysis • group 1 'at risk of HSV-2' (n=13): women seronegative for HSV-2; partner seropositive for HSV-2 • group 2 'at risk for HSV-1' (n=35): women seronegative for HSV-1; partner seropositive for HSV-1 • group 3 'unknown risk' (n=94): women seronegative for HSV-2 and/or HSV-1; partner not tested • group 4 'not at risk' (n=145): women with the same HSV status as their partner The median number of days of observation was 82 (range 30 to 235). There were 20,170 diary-days available for analysis **Unprotected sex acts performed per diary month** **Number of events** / **Group 1: 'at risk of HSV-2'** / **Group 2: 'at risk of HSV-1'** / **Group 3: 'unknown risk'** / **Group 4: 'not at risk'** 0 / 54% / 34% / 31% / 31% 1-3 / 38% / 29% / 37% / 39% >3 / 8% / 37% / 32% / 30% Rate of unprotected genital sex was significantly lower for women at risk of HSV-2 (2.1%) compared to women not at risk (7.8%) (relative risk (RR) 0.3 95%CI 0.1 to 0.8) and compared to women of unknown risk (10.9%) (RR 0.2 95%CI 0.1 to 0.8) Women at risk of HSV-2 infection were more likely to always use a condom (40%) compared to women not at risk (6%) and women of unknown risk (4%) (p=0.005) Women at risk of HSV-2 infection were more likely to receive oral sex (3.5%) than women who were not at risk (1.0%) (RR 3.5 95%CI 1.5 to 8.2). There was no significant difference compared to women at unknown risk There was no significant difference in rate of unprotected genital sex for women at risk of HSV-1 compared to women not at risk or women of unknown risk There were no significant differences in frequency of genital sex or in rates of giving oral sex for women at risk of HSV-1 or HSV-2, or in rates of receiving oral sex for women at risk of HSV-1 compared to women not at risk or of unknown risk
Quality appraisal	The study was assessed using the CASP cohort study checklist. This was a small study and level of participation in follow-up was used as an exclusion criteria. It is therefore not clear how generalisable the results would be to a general population. The results were based on self-reported sexual activity.

Key question 5: Is there an effective intervention for reducing vertical transmission of HSV from mother to child?

Table 20. Hollier & Wendel (2008)[17]

Publication	Hollier LM. Wendel GD. Third trimester antiviral prophylaxis for preventing maternal genital herpes simplex virus (HSV) recurrences and neonatal infection. Cochrane Database of Systematic Reviews 2008, Issue 1 Art. No.: CD004946
Study details	Systematic review of third trimester antiviral prophylaxis
Study objectives	To assess the effectiveness of antenatal antiviral prophylaxis for recurrent genital herpes on neonatal herpes and maternal recurrence at delivery
Inclusions	Randomised controlled trials (RCT) published up to February 2007
Exclusions	None stated
Population	Pregnant women in the third trimester diagnosed with genital herpes infection before or during pregnancy. In all of the included studies, prophylaxis treatment began from 36 weeks
Intervention	Oral antivirals for prophylaxis for recurrent genital herpes at delivery
Comparator	Placebo or no intervention
Outcomes	7 RCTs were included (n=1,249): • 4 compared acyclovir to placebo • 1 compared acyclovir to no treatment • 2 compared valacyclovir to placebo There were no cases of symptomatic neonatal herpes in the intervention or control groups in any of the included studies. 4 studies reported the results of neonatal surface cultures and/or polymerase chain reaction. 2 infants in the treatment group and 1 in the placebo group had virus detected after delivery but all 3 were asymptomatic. There was insufficient evidence to assess the impact of antiviral prophylaxis on neonatal herpes **Meta-analysis** • antiviral prophylaxis associated with significantly less recurrence of genital herpes at delivery (relative risk (RR) 0.28 95%CI 0.18 to 0.43, I^2=0%), equating to an absolute risk reduction of 10.7% • antiviral prophylaxis associated with significantly less HSV detected at delivery (RR 0.14 95%CI 0.05 to 0.39, I^2=0%), equating to an absolute risk reduction of 5.8% • antiviral prophylaxis associated with significantly fewer Caesarean deliveries (RR 0.30 (95%CI 0.20 to 0.45, I^2=27%), equating to an absolute risk reduction of 10.1% The number of women who would need to receive antiviral prophylaxis from 36 weeks until delivery was: • 10 to prevent a recurrence at delivery • 17 to prevent viral detection at delivery • 10 to prevent a Caesarean delivery **Safety** 2 studies reported maternal safety • no difference between intervention and control for maternal renal function (1 study) • no evidence of haematological or biochemical toxicity (2 studies) • symptoms (eg nausea, headache, rash) reported by 13 women in the placebo group and 2 in the intervention group (1 study)

	2 studies reported neonatal safety • 1 study reported a higher mean level of a liver enzyme (aspartate aminotransferase) in the placebo group, but another study reported no difference in the number of infants with liver enzymes (transaminases) greater than 2 standard deviations above the mean • there were no significant differences in other neonatal outcomes
Quality appraisal	The review was assessed using the CASP systematic review checklist. There were no areas of concern in the design and reporting. It is notable that the included studies were small and that 3 of the 7 were terminated early due to slow enrolment. The included studies were from the US, UK and France. The review authors assessed the quality of the included studies using Cochrane guidelines. Six of the 7 studies blinded participants and providers, although blinding of outcome assessors was not performed in 1 study and was unclear in 4 others. The generation of random allocation sequence was considered adequate in 5 studies and unclear in 2. The loss to follow-up was considered zero or negligible in 5 studies and the loss of 10% and 18% in the remaining 2 studies was considered non-differential.

Table 21. Nakubulwa et al (2017)[18]

Publication	Nakubulwa S. Kaye DK. Bwanga F. et al. Effect of suppressive acyclovir administered to HSV-2 positive mothers from week 28 to 36 weeks of pregnancy on adverse obstetric outcomes: a double-blind randomised placebo-controlled trial. Reproductive Health 2017, 14:31
Study details	Double-blind randomised controlled trial (RCT) comparing antiviral prophylaxis to placebo
Study objectives	To determine the effect of oral antiviral prophylaxis administered from 28 to 36 weeks gestation on obstetric outcomes
Inclusions	HSV-2 seropositive women aged 18 to 43 years at 28 weeks gestation
Exclusions	Active genital herpetic lesions High medication burden
Population	200 HSV-2 positive pregnant women at 28 weeks gestation, treated at 1 hospital in Uganda between 2014 and 2015. Women were screened for HSV-2 between 20 and 26 weeks gestation
Intervention	Acyclovir 400mg twice daily from 28 gestation (n=100)
Comparator	Placebo from 28 to 36 weeks gestation (n=100) All patients received acyclovir from 36 weeks gestation
Outcomes	• no significant difference in the incidence of premature rupture of membranes by 36 weeks between the intervention (4.0%) and placebo groups (10.0%) (relative risk (RR) 0.35 95%CI 0.11 to 1.10, p=0.073) (primary outcome) • significant reduction in the incidence of preterm delivery (<37 weeks) in the intervention group (11.1%) compared to the placebo group (23.5%) (RR 0.41 95%CI 0.20 to 0.85, p=0.016) • no significant difference in HSV-2 shedding between intervention and placebo (10.3% vs 12.0%) (RR 0.55 95%CI 0.22 to 1.42, p=0.22) or low birth rate (8.0% vs 15.0%) (RR 0.43 95%CI 0.18 to 1.02, p=0.056) • significant reduction in admission to special care unit in the intervention group (9.0%) compared to placebo (17.3%) (RR 0.43 95%CI 0.19 to 0.96, p=0.040) **Safety** There were no serious adverse events. There was no difference in adverse drug reactions or side effects between the groups

Quality appraisal	The study was assessed using the Cochrane Collaboration's tool for assessing risk of bias in RCTs. There were no concerns relating to the selection, randomisation or blinding of participants and researchers or the reporting of results. An intention to treat analysis was performed. The primary outcome was assessed in all women at 36 weeks. About 90% of participants in each group took the study medication for ≥4 weeks. 50% of women in the intervention group and 54% of women in the placebo group fully complied with the study medication schedule. Delivery outcomes were not available for 3 women (1 in the intervention group and 2 in the placebo group). Results for HSV-2 shedding were available for 161 women. This small study was set in Uganda in a population with high HSV-2 prevalence (over 60.0% in pregnant women). This may limit the applicability of the results to a UK context.

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 22.

Table 22. 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,	13

		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.	14
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*.	16-17
2.3	Appraisal for quality/risk of bias tool	Details of tool/checklist used to assess quality, eg QUADAS 2, CASP, SIGN, AMSTAR.	18
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.	18
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 and Appendix 2
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.	14
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.	19,21,25,29,31
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.	24,28,33
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'?	20,21,26,30,32
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?	35
6.2	Limitations	Discuss limitations of the available evidence and of the review methodology if relevant.	35

References

[1] Looker KJ. Magaret AS. May MT. et al First estimates of the global and regional incidence of neonatal herpes infection. Lancet Global Health 2017, 5: e300-09
[2] Patel R. Green J. Clarke E. et al. 2014 UK national guideline for the management of anogenital herpes. International Journal of STD & AIDS 2015, 26(11): 763-76
[3] Peckham C. Antenatal screening for HSV-1 and -2 infection to prevent neonatal herpes infection. September 2006
[4] Batra D. Davies P. Manktelow BN. Smith C. The incidence and presentation of neonatal herpes in a single UK tertiary centre, 2006-2013. Arch. Dis. Child 2014, 99: 916-921
[5] Vyse AJ. Gay NJ. Slomka MJ. The burden of infection with HSV1 and HSV2 in England and Wales: implications for the changing epidemiology of genital herpes. Sexually Transmitted Infections 2000, 76(3): 183-7
[6] Foley E. Clarke E. Beckett VA.et al. Management of genital herpes in pregnancy, October 2014
[7] US Preventative Services Task Force. Final recommendation statement. Genital herpes infection: serologic screening. Available from https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/genital-herpes-screening1 (Accessed March 2018)
[8] Marchi S. Trombetta CM. Gasparini R. Temperton N. Montomoli E. Epidemiology of herpes simplex virus type 1 and 2 in Italy: a seroprevalence study from 2000 to 2014. J. Prev Med. Hyg. 2017, 58: E27-E33
[9] Puhakka L. Sarvikivi E. Lappalainen M. Surcel HM. Saxen H. Decrease in seroprevalence for herpesviruses among pregnant women in Finland: cross-sectional study of three time points 1992, 2002 and 2012. Infectious Diseases 2016, 48 (5): 406-410
[10] Kucera P. Gerber S. Marques-Vidal P. Meylan PRA. Seroepidemiology of herpes simplex virus type 1 and 2 in pregnant women in Switzerland: an obstetric clinic based study. European Journal of Obstetrics & Gynecology and Reproductive Biology 2012, 160: 13-17
[11] Sauerbrei A. Schmitt S. Scheper T. et al. Seroprevalence of herpes simplex virus type 1 and type 2 in Thuringia Germany, 1999 to 2006. Euro Surveill. 2011, 16(44): pii=20005
[12] Berntsson M. Tunbäck P. Ellström A. Krantz I. Löwhagen GB. Decreasing prevalence of herpes simplex virus-2 antibodies in selected groups of women in Sweden. Acta Derm. Venerol 2009, 89: 623-626
[13] Sasadeusz JJ. Silvers JE. Kent HE. et al. Prevalence of HSV-2 antibody in a Melbourne antenatal population attending a tertiary obstetric hospital. Australian and New Zealand Journal of Obstetrics and Gynaecology 2008, 48: 266-272
[14] Xu F. Markowitz LE. Gottlieb SL. Berman SM. Seroprevalence of herpes simplex virus types 1 and 2 in pregnant women in the United States. Am. J. Obstet. Gynecol 2007, 196 (43): e1-43.e6
[15] Leyland B. Kennedy MR. Wimberly YH. Levine BJ. Cherpes TL. Serologic detection of herpes simplex virus type 2 antibodies among pregnant women using a point-of-care test from Focus Diagnostics. J. Clin. Virol. 2009, 44(2): 125-128
[16] Delaney S. Gardella C. Daruthayan C. et al. A prospective cohort study of partner testing for herpes simplex virus and sexual behaviour during pregnancy. JID 2012, 206: 486-494
[17] Hollier LM. Wendel GD. Third trimester antiviral prophylaxis for preventing maternal genital herpes simplex virus (HSV) recurrences and neonatal infection. Cochrane Database of Systematic Reviews 2008, Issue 1 Art. No.: CD004946
[18] Nakubulwa S. Kaye DK. Bwanga F. et al. Effect of suppressive acyclovir administered to HSV-2 positive mothers from week 28 to 36 weeks of pregnancy on adverse obstetric outcomes: a double-blind randomised placebo-controlled trial. Reproductive Health 2017, 14:31