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Serological Screening for Genital Herpes: A Reaffirmation Evidence Update for the U.S. Preventive Services Task Force

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Structured Abstract

Purpose: To systematically review the recent evidence on (1) benefits and harms of serologic screening for herpes simplex virus-2 (HSV-2) genital herpes infection in adolescents and adults, (2) accuracy of serologic screening tools, and (3) benefits and harms of interventions for screen-detected or recently diagnosed genital herpes for the U.S. Preventive Services Task Force (USPSTF) to update its 2016 recommendation.

Data Sources: PubMed/MEDLINE, the Cochrane Library, Embase, and trial registries from September 30, 2015, through January 16, 2022; reference lists of retrieved articles; outside experts; and reviewers, with surveillance of the literature through September 23, 2022.

Study Selection: English-language randomized, controlled trials (RCTs) comparing screening with no screening in persons without past or current symptoms of genital herpes, studies evaluating accuracy, benefits, and harms of serologic screening tests for HSV-2, RCTs assessing preventive interventions in asymptomatic persons seropositive for HSV-2.

Data Analysis: Two reviewers independently evaluated all abstracts and articles and rated study quality using predefined criteria.

Results: We dually reviewed 3,119 abstracts and 64 full-text articles against a priori eligibility criteria. No new eligible studies were identified.

Limitations: Our review was designed to identify evidence that could result in a change in the 2016 USPSTF D recommendation; therefore, it targeted only those studies published since 2016 that are relevant to serologic screening in persons without past or current symptoms of genital herpes.

Conclusions: Our focused evidence update did not identify any new eligible studies on the benefits or harms of serologic screening for HSV-2, accuracy of available HSV-2 serologic tests, or preventive interventions that could be used in asymptomatic persons seropositive for HSV-2 to reduce morbidity and transmission of genital herpes. Foundational evidence that informed the 2016 USPSTF recommendation suggests that serologic screening for genital herpes is associated with a high rate of false-positive test results and potential psychosocial harms.

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Chapter 1. Introduction

Scope and Purpose

The Agency for Healthcare Research and Quality (AHRQ) has requested a limited systematic review update focused on screening and treatment of asymptomatic genital herpes simplex virus-2 (HSV-2) in the general population. The report will be used by the United States Preventive Services Task Force (USPSTF) to update its 2016 recommendation on this topic. In 2016, the USPSTF concluded the current evidence was adequate to recommend against serologic screening for genital herpes infection (D recommendation). The USPSTF estimated benefit at no greater than small and harms as at least moderate. This 2021 report systematically evaluates the new evidence on serologic screening for genital herpes. Consistent with the prior review, the scope for serologic screening is limited to HSV-2 because serologic screening in asymptomatic populations for HSV-1 cannot distinguish between orofacial and anogenital disease.

Condition Definition

Genital herpes is a viral sexually transmitted infection (STI) caused by one of two HSV subtypes: HSV-1 or HSV-2. Once acquired, HSV viral latency is established in the sacral ganglia followed by viral reactivation and recurrent local disease. The term "genital herpes" refers to a range of signs and symptoms of HSV infection in the area innervated by the sacral nerve ganglion, usually genital ulcers or vesicular lesions sometimes associated with other local symptoms (e.g., itching, dysuria) or systemic symptoms such as fever.[1, 2] Diagnosis of genital herpes is based on clinical presentation and often confirmed by testing of a swab specimen of a genital lesion.

For purposes of this review, the term "asymptomatic" refers to individuals with no known past or current history of genital herpes. This can include individuals who may have unrecognized genital herpes, either because symptoms are very mild or because symptoms are attributed to other causes (e.g., urinary tract infection). Individuals previously diagnosed with genital herpes who are not currently experiencing symptoms (i.e., an asymptomatic period following an outbreak of genital herpes) are not considered asymptomatic in this review.

HSV-1 is most commonly associated with orofacial herpes (e.g., "cold sores") and usually acquired during childhood but can also cause genital herpes. HSV-2 accounts for most prevalent cases of genital herpes and is more likely to cause frequent symptomatic recurrences and more severe symptoms than HSV-1 infection.[3]

Incidence, Prevalence, and Burden

Incidence and Prevalence

Genital herpes is one of the most prevalent STIs in the United States. Based on estimates from the National Health and Nutrition Examination Survey (NHANES) 2015–2016 data, the age-adjusted seroprevalence of HSV-2 among U.S. adults (ages 14 to 49 years) was 12.1 percent and HSV-1 seroprevalence was 48.1 percent.[4] Additionally, it is estimated that 22 percent of pregnant persons may be HSV-2 seropositive.[5] It is important to note that not all persons who are HSV seropositive experience symptoms of genital herpes, and many persons who are HSV-1 seropositive may only experience orofacial herpes or may not have symptoms at all. The estimated prevalence of genital herpes using NHANES HSV-2 seroprevalence data from 2015–2018 is a median of 18.6 million cases (interquartile range [IQR] 18.1 to 19.0 million) among U.S. adults ages 18 to 49 years and approximately 572,000 yearly incident cases (IQR 479,000 to 673,000).[6] Estimating the additional burden of prevalent and incident genital herpes due to HSV-1 is difficult because data on persons who are HSV-1 seropositive and experience symptoms of genital herpes are very limited. However, assuming 5 percent of those who are simultaneously HSV-1 seropositive and HSV-2 seronegative have a genital HSV-1 infection, it is estimated there would be an additional 3.0 million prevalent and 35,000 incident infections (based on 2018 data).[6] Importantly, both HSV-1 and HSV-2 seroprevalences have steadily decreased over the past two decades.[4, 6-8]

Estimates of HSV seroprevalence vary by age, sex, race and ethnicity, and geographic region. HSV-2 seroprevalence increases with age from 0.8 percent (ages 14 to 19 years) to 21.2 percent (ages 40 to 49 years);[4] HSV-1 seroprevalence estimates for similar age groups range from 27.0 percent to 59.7 percent.[4] While HSV-1 is nearly 30 times more common than HSV-2 among adolescents, that gap narrows substantially to approximately threefold among middle-aged adults.

Although HSV-1 is still most commonly associated with orofacial herpes, the epidemiology of genital herpes is changing such that an increasing proportion of new genital infections are due to HSV-1 rather than HSV-2 transmission. This shift is thought to be related to changing sexual practices and lower rates of HSV-1 acquisition earlier in life (and thus less protection against acquiring HSV-1 genital herpes after becoming sexually active). For example, in a retrospective review of 675 HSV cultures collected from U.S. college students of both sexes at a student health clinic, HSV-1 was isolated from 78 percent of genital herpes infections in 2001 compared with just 31 percent in 1993.[9] In another study following seronegative women ages 18 to 30 years in the control arm of an HSV vaccine trial conducted from 2003 to 2007 in the U.S. and Canada, of the 183 participants who became infected with HSV, 49 subsequently developed symptomatic genital herpes: 28 (57%) from HSV-1 and 21 (43%) from HSV-2 infection.[10]

Individuals with HSV infection of one serotype can develop a new infection from the other serotype, which is known as a nonprimary infection (prevalent primary HSV-1 infection with new, nonprimary HSV-2 infection, or vice versa). However, the incidence of nonprimary genital herpes among previously asymptomatic persons is unknown. Although it is difficult to estimate

the incidence of nonprimary HSV infection, one study conducted in a Parisian sexually transmitted disease clinic between 1999 and 2002 enrolled 248 participants with active genital herpes. HSV-2 first nonprimary infection (i.e., HSV-2–positive culture or polymerase chain reaction [PCR]), HSV-1 seropositive, and HSV-2 seronegative) was reported in 22 participants, and there were no cases of HSV-1 first nonprimary infection.[11]

HSV-2 seroprevalence in women is nearly twice that of men (15.9% vs. 8.2%), which is attributed to anatomic factors predisposing women to be more susceptible to HSV-2 infection than men. However, HSV-1 seroprevalence is more closely matched between women (50.9%) and men (45.2%).[4] Likewise, men who have sex with men also have an HSV-2 seroprevalence twice that of the general population of men.[12, 13]

Based on reporting of the NHANES 2015-2016 survey, non-Hispanic Black persons have the highest estimated seroprevalence of HSV-2 infection (34.6%), which is approximately four times that of non-Hispanic White persons (8.1%) and Mexican American persons (9.4%).[4] Estimated HSV-1 seroprevalence is highest among Mexican American persons (71.7%) compared with non-Hispanic Black persons (58.8%) and non-Hispanic White persons (36.9%). Although HSV seroprevalence has declined over time for all these groups, racial and ethnic disparities remain.[7, 8]

Burden

Genital HSV infection can lead to both acute and chronic morbidity. **Table 1** outlines the clinical features of primary (no prior HSV exposure), recurrent (HSV seropositive for the presenting HSV type), and nonprimary (HSV seropositive for the nonpresenting HSV type) infection. Acute primary infection can be severe and associated with multiple, bilateral, ulcerating, pustular lesions that resolve after a mean duration of 19 days.[14] Extragenital complications can also occur; in a study of 268 adults with primary genital herpes, extragenital complications included distant skin lesions (20%), secondary yeast infections (11%), aseptic meningitis (8%), and urinary bladder retention due to sacral autonomic nervous system dysfunction (2%).[14] An estimated 70 to 90 percent of patients with clinical first episodes of genital HSV-2 will experience recurrences in the first year and many will have multiple symptomatic episodes per year; the mean number is 4, but some patients may have 10 or more.[1, 15] Recurrences are more common with HSV-2 than HSV-1.[16, 17] Over time, the average number of symptomatic recurrences per year declines.[15, 16] Recurrent infection often includes ulcerative or vesicular lesions sometimes associated with a prodrome of local itching, tingling, or pain. These episodes are usually milder and shorter in duration than primary infection and can be subclinical or entirely asymptomatic. Nonprimary first-episode infection is associated with fewer lesions and less systemic symptoms than primary infection, presumably because the presence of antibodies against one HSV type offers some protection against the other.[14, 18]

Genital HSV-2 infection is highly prevalent among patients with human immunodeficiency virus (HIV)-infection. Epidemiologic studies suggest that prevalent and incident genital HSV-2 increases the risk of HIV acquisition,[19-23] potentially due to disruption of the genital mucosal barrier or alteration of immunologic factors (or both). In addition, genital HSV-2 infection may contribute to the risk of HIV transmission by increasing HIV genital shedding (particularly at sites of genital ulcerations).[24] Whether this association results from similar modes of acquisition

or is due to biologic interactions between the two viruses has been a topic of debate. So far, clinical trials have not supported a role for HSV-2 suppressive therapy in preventing HIV acquisition among HSV-2 seropositive HIV-uninfected persons.[25, 26]

Studies indicate that most persons who are seropositive for HSV-2 are expected to shed HSV from the genital tract at some point even without symptoms.[27-29] For example, in a study of 308 HSV-2 seropositive persons who collected daily genital swabs for at least 30 days (n=19,082 collected swabs), 3,664 (19%) were HSV positive by PCR. The mean duration of shedding per episode was 3.6 days, and the mean time between episodes was 9.4 days. Although it is difficult to estimate the rate of HSV-2 acquisition due to asymptomatic viral shedding, one study of 741 serodiscordant couples reported 27 (3.6%) new HSV-2 infections over the 8-month study period. In a subset of HSV seropositive source partners, genital swabs collected daily for 2 months were positive for HSV on 10.8 percent of the days; shedding was detected in 82 percent of participants.[30] However, it is unknown how frequently persons with asymptomatic HSV-2 infection (i.e., HSV-2 seropositive but no clinical history of genital herpes) transmit the disease during periods of viral shedding.

Approximately half of persons with symptomatic recurrences have prodromal symptoms before eruption of genital lesions (e.g., local mild tingling or shooting pains in the buttocks, legs, and hips).[18, 31] Because of the chronic nature of genital HSV, those with symptomatic infections often experience psychological distress following diagnosis.[32] Common concerns for patients include the potential for ongoing symptomatic episodes, the impact of herpes on sexual relationships, questions about transmission to sexual partners, and management of herpes in pregnancy.[32]

Neonatal HSV

Genital HSV infection during pregnancy is of particular concern because of the risk of vertical transmission to the infant during delivery and because of the significant morbidity and mortality associated with neonatal herpes. Vertical transmission typically occurs by direct contact with the virus in the genital tract during delivery. Importantly, risk of vertical transmission is higher among women who acquire a new genital infection late in pregnancy.[33] Similar proportions of neonatal HSV infections may be due to HSV-1 and HSV-2, with a slight preponderance of cases attributable to HSV-1 because postnatal transmission from individuals with orofacial herpes can also occur.[34, 35] Among newborns diagnosed with herpes, approximately 45 percent of cases involve infection of the skin, eye, and mucous membranes; 30 percent develop the encephalitic form of neonatal herpes, which presents with nonspecific signs and symptoms such as fever, lethargy and irritability, or poor feeding; and 25 percent develop disseminated disease.[36] Many survivors of central nervous system neonatal herpes infection are left with long-term neurodevelopmental impairment.[37] Approximately 30 percent of infants with disseminated disease and 4 percent with central nervous system disease will die from HSV infection.[18]

The incidence of neonatal HSV infection is challenging to estimate because it is not reportable in many states and appears to vary by insurance status and region. The most recent U.S. multistate study reporting the incidence of HSV infection examined Medicaid claims data from 12 states and reported an increase from 3.4 to 5.5 per 10,000 live births between 2009 and 2015,[38] which is an increase from a prior report in 2006 of 1.0 cases per 10,000 live births.[39] Using estimates

for U.S. live births in 2015, that translates to approximately 2,200 cases in that year.[40] However, because HSV incidence appears to vary by insurance status (e.g., 0.5 cases per 10,000 live births among the privately insured population and 1.5 cases per 10,000 live births among infants covered by Medicaid[38]), that is likely an overestimate of annual neonatal HSV cases.

Rationale for Serologic Screening

In theory, serologic screening to identify unrecognized HSV-2 infection followed by appropriate counseling or treatment could prevent transmission to sexual partners and neonates and reduce future morbidity from symptomatic recurrences. Episodic or suppressive antiviral treatment for HSV-2 infection may be prescribed to reduce symptomatic episodes and shedding. In pregnant persons, serologic screening to identify seronegative persons followed by appropriate counseling could reduce neonatal HSV infection given that persons who acquire HSV late in pregnancy and who are seronegative at delivery are at highest risk for vertical transmission.

Several U.S. Food and Drug Administration (FDA)-approved type-specific HSV serologic tests exist to identify genital herpes. Importantly, it may take 6 weeks to 3 months after infection for the antibody response these tests detect to occur.[41] While HSV-2 seropositivity almost universally indicates anogenital infection, HSV-1 seropositivity can indicate either orofacial or anogenital disease.[42] For this reason, serologic testing for HSV-1 cannot be used to identify asymptomatic genital herpes. Therefore, screening for asymptomatic genital herpes, if it were found to be beneficial, would be limited to HSV-2 serologic testing.

Currently, the criterion standard for HSV-2 confirmatory testing is the Western blot. However, the University of Washington Virology Laboratory is the only U.S. site currently offering this test, which is not universally available, thereby limiting the availability of confirmatory testing.

For persons diagnosed with genital herpes, treatment with FDA-approved systemic antiviral medications (acyclovir, valacyclovir, and famciclovir) can partially reduce genital herpes symptoms when used to treat first clinical and recurrent episodes or when used as daily suppressive therapy. However, these medications are not curative and do not change the frequency or severity of future recurrences after the medication is discontinued. Most evidence supporting the benefit of daily suppressive therapy comes from trials enrolling populations who have frequent symptomatic recurrences of genital herpes (>4 episodes per year), and the magnitude of effect in this population is somewhat uncertain. For example, a 2014 Cochrane review (22 randomized, controlled trials [RCTs]) evaluating the efficacy of antiviral medications to suppress genital herpes outbreaks in nonpregnant adults concluded that there was low-quality evidence that the risk of having at least one clinical recurrence over 2 to 12 months was reduced with acyclovir (9 parallel trials; n=2,049; relative risk [RR], 0.48 [95% confidence interval {CI}, 0.39 to 0.58]), valacyclovir (4 trials; n=1,788; RR, 0.41 [95% CI, 0.24 to 0.69]), or famciclovir (2 trials; n=732; pooled RR, 0.57 [95% CI, 0.50 to 0.64]).[43] It is unclear whether these results would apply to persons who have less frequent recurrences or who are asymptomatic.

Recommendations of Other Organizations

Guidelines from prominent U.S. and international organizations, including the American College of Obstetrics and Gynecology (ACOG), recommend against routine serologic screening for genital herpes in asymptomatic adults and adolescents (**Table 2**).[44-51] However, several of these groups do recommend targeted screening in select patient populations. The Centers for Disease Control and Prevention (CDC) and International Union Against Sexually Transmitted Infections (IUSTI) advise that serologic screening may be useful in individuals whose sexual partners have a history of genital herpes because serodiscordant couples may benefit from counseling regarding behavioral strategies and suppressive therapy with antiviral medications to prevent transmission.[49, 51] Furthermore, the CDC recommends clinicians consider asymptomatic screening among persons with HIV infection at their initial evaluation to inform discussions regarding suppressive medication given the risk of more severe recurrent episodes of genital herpes among immunocompromised individuals.[51] However, clinicians are advised to first ask about a history of genital symptoms indicative of HSV infection, and so this recommendation primarily pertains to diagnosis not screening. Because the accuracy of commercially available HSV-2 tests is modest, the 2021 CDC STI Treatment Guidelines suggest confirmatory testing for diagnostic purposes using either the BioKit EIA or Western blot testing.[51]

Owing to the risk of vertical transmission and the severe morbidity associated with neonatal HSV infection, most guidelines make specific recommendations related to the prevention, diagnosis, and management of genital herpes in pregnancy. Recommendations against routine serological screening remain unchanged from the general population among all organizations, including ACOG. However, the CDC, Society of Obstetricians and Gynaecologists of Canada (SOGC), and IUSTI recommend asking people early during pregnancy about a personal history of genital herpes and reserving serologic screening for asymptomatic individuals whose partner has a history of genital herpes.[47, 49, 51] Seronegative individuals should then be advised to abstain from vaginal intercourse or receptive oral intercourse during the third trimester with a partner with a known history of genital or orofacial herpes, respectively. The goal of this recommendation is to prevent the development of primary genital herpes infection in the third trimester when the risk of vertical transmission is highest, and it focuses on behavioral counseling rather than pharmacologic treatment because there is no evidence showing reduced transmission between serodiscordant partners specifically during pregnancy.

Additional pregnancy-related recommendations from ACOG and other organizations focus on diagnostic testing, antiviral medication use, and delivery management. Interventions to reduce the risk of neonatal transmission include the use of suppressive antiviral therapy after 36 weeks' gestation for pregnant individuals with recurrent genital herpes or a first episode of genital herpes during pregnancy and pursuing cesarean delivery for individuals with active infections or prodromal symptoms at the time of delivery. Decisions regarding these interventions depend on a history of symptomatic genital herpes infection such that the identification of asymptomatic infection through serologic screening should not alter management decisions.

Current Clinical Practice in the United States

Data on actual screening practices for genital herpes in the United States are limited. In one study conducted at a single State health department STI clinic in 2008, 12.7 percent of individuals chose to undergo serologic evaluation for HSV-2 when it was routinely offered.[52] Older studies from the United Kingdom and Australia described the routine availability of type-specific HSV serologic screening at STI clinics as well.[53-55] It is worth noting that the testing rates and practices observed in these studies are not representative of general practice given that they were all conducted in STI clinics and, in some cases, report combined asymptomatic screening and diagnostic testing rates. Furthermore, most were conducted before the widespread availability of polymerase chain reaction testing for suspected lesions and before updated guidelines from the USPSTF and other organizations advising against routine screening. Therefore, these results are unlikely to provide an accurate snapshot of current clinical practice.

Chapter 2. Methods

Key Questions and Analytic Framework

Using USPSTF methods, the Evidence-based Practice Center (EPC) investigators, USPSTF members, and Agency for Healthcare Research and Quality (AHRQ) Medical Officers developed the scope and key questions (KQs). The analytic framework and KQs that guided the review are shown in **Figure 1**. Seven KQs were developed for this focused evidence update:

1. Does serologic screening for herpes simplex virus type 2 (HSV-2) or combined testing for herpes simplex virus type 1 (HSV-1) and 2 in asymptomatic adolescents and adults reduce future symptomatic episodes and transmission of genital herpes, including vertical transmission for pregnant persons?
2. What is the accuracy of serologic screening for HSV-2 in asymptomatic adolescents, adults, and pregnant persons?
3. What are the harms of serologic screening for HSV-2 or combined testing for HSV-1 and HSV-2 in asymptomatic adolescents, adults, and pregnant persons?
4. How effective are antiviral medications in reducing genital HSV-2 viral shedding in asymptomatic adolescents, adults, and pregnant persons?
5. How effective are antiviral medications and behavioral counseling interventions in reducing future symptomatic episodes and transmission of genital herpes in asymptomatic adolescents and adults, including vertical transmission for pregnant persons?
6. What are the harms of antiviral medications and behavioral counseling interventions for reducing future symptomatic episodes and transmission of genital herpes in asymptomatic adolescents and adults, including vertical transmission for pregnant persons?
7. What is the evidence supporting an association between subclinical genital HSV-2 viral shedding and health outcomes in asymptomatic adolescents, adults, and pregnant persons who are seropositive for HSV-2?

In addition to addressing the KQs, this review also looked for evidence related to two contextual questions that focused on (1) the proportion of asymptomatic adults, adolescents, and pregnant persons identified as being seropositive for HSV-2, HSV-1, or both that will have a recognized symptomatic episode of genital herpes and (2) the availability of externally validated, reliable risk stratification tools that distinguish persons who are more or less likely to have genital herpes. These contextual questions were not part of our systematic review. They are intended to provide additional background information. Literature addressing these questions is summarized in **Appendix A**.

Data Sources and Searches

We searched PubMed/MEDLINE, the Cochrane Library, and Embase for English-language articles published from September 30, 2015, through January 16, 2022. Medical Subject

Headings were used as search terms when available and keywords when appropriate, focusing on terms to describe relevant populations, tests, interventions, outcomes, and study designs. Complete search terms and limits are detailed in **Appendix B1**. Targeted searches for unpublished literature were conducted by searching ClinicalTrials.gov, the FDA's Drugs@FDA and Devices@FDA websites, and the World Health Organization International Clinical Trials Platform Registry. To supplement electronic searches, reference lists of pertinent articles, studies suggested by reviewers, and comments received during public commenting periods were reviewed. This search was updated during the peer review process by applying the same search strategies, limited from the date of the original searches to the present. Studies suggested by peer reviewers or public comment respondents were also reviewed using the same inclusion and exclusion criteria to determine if the new citations should be incorporated into the review. We conducted active surveillance of the literature through article alerts and targeted searches of journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation. All literature search results were managed using EndNote™ version 9.2 (Thomson Reuters, New York, NY).

Study Selection

Inclusion and exclusion criteria for populations, interventions, comparators, outcomes, settings, and study designs were developed with input from the USPSTF (**Appendix B2**). Two reviewers independently screened titles and abstracts of all identified articles using Covidence systematic review software (Veritas Health Innovation Ltd, Melbourne, Australia).[56] Two reviewers then independently screened the full texts to determine final inclusion or exclusion, and disagreements were resolved by discussion and consensus.

We included English-language studies of immunocompetent adults or adolescents age 13 years or older, including pregnant persons. For all KQs, studies of persons who did not have symptoms or a clinical history of genital herpes were eligible, as were studies of asymptomatic partners of persons with known genital herpes (i.e., serodiscordant couples). For KQ 1 (direct evidence that screening improves health outcomes), we included only randomized, controlled trials (RCTs) comparing groups that were screened with groups that were not screened.

For KQ 2 (screening test accuracy), we searched for studies that assessed the accuracy of FDA-approved serologic tests for HSV-2 (e.g., sensitivity, specificity) compared with the Western blot. The Western blot has been used as a criterion standard in studies assessing commercially available serologic tests in the United States. For this KQ alone, studies including symptomatic individuals were eligible as long as the study population was not selected based on symptoms or a diagnosis of genital herpes (i.e., included both asymptomatic and symptomatic individuals). We excluded studies using tests that were not serologic (e.g., viral culture), not type specific, and not commercially available or FDA approved. We included studies assessing type-specific combination tests (i.e., those simultaneously reporting HSV-1 and HSV-2), but we did not assess the accuracy of HSV-1 testing. Good-quality, recent (within 5 years) systematic reviews were eligible, as well as trials or observational studies published since the most recent review for the USPSTF.

For KQ 3 (harms of screening), we included studies assessing the harms of screening in populations that are clearly asymptomatic (i.e., no current symptoms) and with no prior diagnosis of genital herpes and with or without a comparison group; eligible harms outcomes included labeling, anxiety, stigma, and others (**Appendix B2**). Good-quality, recent (within 5 years) systematic reviews were eligible, as well as trials and observational studies published since the most recent review for the USPSTF.

Studies assessing benefits or harms of preventive medications for HSV-2 (KQs 4–6) and RCTs comparing FDA-approved oral antiviral medications for the suppression of recurrent genital HSV (i.e., acyclovir, famciclovir, or valacyclovir) with placebo were eligible. RCTs of behavioral counseling interventions (e.g., education or counseling; partner notification; barrier protection, such as condom use; or combinations of these components) were also eligible for KQs 5 and 6. For studies assessing the harms of antiviral medications in pregnant persons (KQ 6), multi-institution antiviral medication pregnancy exposure registries were also eligible. For studies assessing the benefits of preventive medications and behavioral counseling interventions (KQ 5), eligible outcomes included reduced rates of symptomatic episodes of genital herpes and genital herpes transmission (including measures of HSV-2 seroconversion), rates of neonatal HSV infection, and reduced rates of symptomatic genital herpes at delivery. For KQ 4 (effects of antiviral medication on subclinical HSV-2 shedding), we included any outcome measure of subclinical HSV-2 shedding (e.g., percentage of days with any shedding detected); however, we did not include measures of viral shedding during symptomatic occurrences. Eligible harms outcomes for intervention studies (KQ 6) included medication-related adverse events and psychosocial harms of behavioral counseling interventions.

For all KQs except diagnostic test accuracy (KQ 2), we limited studies to those conducted in countries categorized as "very high" on the United Nations Human Development Index (HDI).[57] This decision was made because data from lower HDI countries would have very limited applicability for most KQs. For diagnostic test accuracy (KQ 2), studies from countries of any HDI category were eligible; most studies of diagnostic test accuracy from the previous review were conducted in African countries.

Quality Assessment and Data Abstraction

Two reviewers independently assessed methodological study quality using predefined criteria developed by the USPSTF and adapted for this topic (**Appendix B3**).[58] We assigned a quality rating of good, fair, or poor according to the USPSTF's study design-specific criteria. Disagreements were resolved through discussion. For studies of diagnostic test accuracy, we assessed the quality of studies as good, fair, or poor using predefined criteria developed by the USPSTF and adapted for this topic (**Appendix B Table 3**).[58] Only studies rated as having good or fair quality were included.

For each included study, one investigator extracted pertinent information about the methods, populations, interventions, comparators, outcomes, timing, settings, and study designs. A second team member reviewed all data extractions for completeness and accuracy.

Data Synthesis and Analysis

This report is a rapid review to provide an overview of evidence published since the USPSTF last considered this topic in 2016. Therefore, it describes the results of newly identified publications only. Results of studies included in previous evidence reviews are not pulled forward into the report, no pooled analyses were conducted, and no new studies were identified. We included a summary table with the conclusions of the previous review (**Table 3**).[59]

Expert Review and Public Comment

A draft research plan for this topic was posted on the USPSTF website for public comment from July 8, 2021, to August 4, 2021. In response to comments, we clarified eligible screening tests by replacing references to "combined testing" and "paired testing" to "type-specific testing." The final version of the research plan was posted on the USPSTF website on November 18, 2021.

A draft report was reviewed by content experts, representatives of Federal partners, USPSTF members, and AHRQ Medical Officers. Reviewer comments were presented to the USPSTF during its deliberations and subsequently addressed in revisions of this report when appropriate. Additionally, a draft of this report was posted for public comment on the USPSTF Web site from August 16, 2022 to September 12, 2022. Few comments were received during this public comment period; a few outdated background references were updated, and an editorial change was made to the report based on these comments, but no changes were made to the included evidence or to our conclusions.

USPSTF and AHRQ Involvement

The authors worked with USPSTF members and AHRQ staff at key points throughout the review process in developing and refining the scope of work. AHRQ staff also provided oversight for the project and reviewed the draft report. The authors are solely responsible for the report's content.

Chapter 3. Results

Literature Search

This review identified 3,119 unique records and assessed 64 full-text articles for eligibility (**Figure 2**). Our review and quality assessment of these articles resulted in no new publications for any KQ. **Appendix C** lists all 64 articles reviewed as full texts and their reasons for exclusion. A single study met all our eligibility criteria except for study quality, which was rated as poor quality, and the details of its quality assessment appear in **Appendix D Tables 1 and 2**. In addition, we present the conclusions of the previous review in a summary table (**Table 3**).[59]

Results by Key Question

KQ 1. Does Serologic Screening for HSV-2 or Combined Testing for HSV-1 and 2 in Asymptomatic Adolescents and Adults Reduce Future Symptomatic Episodes and Transmission of Genital Herpes, Including Vertical Transmission for Pregnant Persons?

We found no eligible studies that addressed this question.

KQ 2. What Is the Accuracy of Serologic Screening for HSV-2 in Asymptomatic Adults, Adolescents, and Pregnant Persons?

We identified no new eligible studies that addressed this question. We did identify a single eligible study that was not included because it was rated poor quality, primarily due to inconsistent application of the reference test.[60] However, the study results would not have changed conclusions about the accuracy of HerpeSelect HSV-2 ELISA because the reported accuracy was consistent with our pooled sensitivity and specificity from the previous review. Details of the quality assessment rating for this study appear in **Appendix D Tables 1 and 2**.

KQ 3. What Are the Harms of Serologic Screening for HSV-2 or Combined Testing for HSV-1 and HSV-2 in Asymptomatic Adolescents, Adults, and Pregnant Persons?

We identified no new eligible studies that addressed this question.

KQ 4. How Effective Are Antiviral Medications in Reducing Genital HSV-2 Viral Shedding in Asymptomatic Adolescents, Adults, and Pregnant Persons?

We identified no new eligible studies that addressed this question.

KQ 5. How Effective Are Antiviral Medications and Behavioral Counseling Interventions in Reducing Future Symptomatic Episodes and Transmission of Genital Herpes in Asymptomatic Adults and Adolescents, Including Vertical Transmission for Pregnant Persons?

We identified no new eligible studies that addressed this question.

KQ 6. What Are the Harms of Antiviral Medications and Behavioral Counseling Interventions for Reducing Future Symptomatic Episodes and Transmission of Genital Herpes in Asymptomatic Adults and Adolescents, Including Vertical Transmission for Pregnant Persons?

We identified no new eligible studies that addressed this question.

KQ 7. What Is the Evidence Supporting an Association Between Subclinical Genital HSV-2 Viral Shedding and Health Outcomes in Asymptomatic Adults, Adolescents, and Pregnant Persons Who Are Seropositive for HSV-2?

We had insufficient evidence to establish the benefit of preventive medications for reducing genital HSV-2 subclinical viral shedding (KQ 4) and, therefore, did not address this KQ.

Chapter 4. Discussion

Summary of Findings and Comparison With Last Review

Our systematic review yielded no relevant new studies that were published since the 2016 review assessing screening for genital herpes. We identified one new diagnostic test accuracy study (KQ 2), but it was not included in the final results because of poor study quality; results of that study would not have meaningfully altered the pooled accuracy estimates for the Focus HerpeSelect HSV-2 ELISA. Therefore, the overall conclusions from this review are unchanged from those of the previous review (**Table 3**). No population-based trials of screening versus no screening for HSV-2 were identified.

In its 2016 review on this topic, the USPSTF concluded the current evidence was adequate to recommend against serologic screening for genital herpes infection in asymptomatic adolescents and adults (D recommendation). Benefits were estimated at no greater than small, and harms were estimated as at least moderate. Driving the harms estimate was the potentially high false-positive rate of current serologic testing and overdiagnosis among true-positive tests. The review estimated that in a population of 10,000 persons with 15 percent HSV-2 prevalence serologic testing would identify 1,585 true-positive and 1,445 false-positive results. In other words, one in two positive results may be false, and the harms associated with these diagnoses included social and emotional harms, in addition to the potential harms of unnecessary preventive antiviral medications. For benefits, the USPSTF based its estimate on the natural history and epidemiology of HSV and the very limited number of controlled studies examining benefits in asymptomatic and pregnant persons. There is currently no available cure for HSV, and the evidence for pharmacologic management to prevent symptomatic outbreaks is uncertain in this population.

Other U.S. and international groups also recommend against routine serological screening of asymptomatic persons in the general population. However, the CDC and IUSTI suggest screening sexual partners of HSV seropositive persons. Likewise, the CDC, IUSTI, and American College of Obstetricians and Gynecologists recommend asking about genital herpes symptoms in pregnant persons and suggest considering serologic screening in pregnant persons with known HSV seropositive sexual partners.

Limitations

Our review was intended to support the USPSTF reaffirmation process and thus includes only the interval evidence accrued since the last recommendation in 2016. Our review was scoped to identify evidence that could result in a change in the prior recommendation and therefore has some limitations. Studies of screening or treatment were limited to only those conducted in countries listed as “very high” on the HDI. This decision was based on the applicability of the populations, testing strategies, treatments, and systems of care found in these countries compared with the United States. Diagnostic test accuracy studies for KQ 2, however, were not limited by

country so long as index and reference tests met our inclusion criteria. We required studies to compare FDA-approved, currently available serologic screening tests with Western blot.

We did not include preventive interventions that are not FDA approved and are currently unavailable in the United States, such as studies of topical tenofovir gel or HSV-2 vaccines. We did not evaluate other comparisons, such as a serologic test compared with a viral PCR swab or culture to diagnose genital herpes. We focused on studies comparing a serologic test with the Western blot and did not include studies that assessed the concordance between two commercially available serologic tests (i.e., without comparing them to a criterion standard).

For benefits, we did not evaluate every possible outcome. For example, we did not include outcomes such as the transmission or acquisition of HIV because other effective strategies of preventing HIV transmission exist,[61-63] and there is limited evidence to support screening for asymptomatic HSV-2 infection in U.S. primary care settings for HIV prevention.

We also limited our assessment to studies enrolling persons who had no current or prior symptoms. For persons with frequent symptomatic recurrences of genital herpes (>4 episodes per year), antiviral medications have been shown to reduce the frequency of recurrences; however, the magnitude of effect is somewhat uncertain, and the quality of evidence is low. Furthermore, it is unclear whether any benefits would apply to persons who have less frequent recurrences or who are asymptomatic.

We only included studies that evaluated asymptomatic populations, defined as those without a clinical history of genital herpes. Studies that included persons with prior HSV infection could be included if there were few cases of genital herpes or if asymptomatic populations were analyzed separately. For example, we excluded a pregnancy registry examining the effect of antiviral agents (i.e., acyclovir, valacyclovir, and famciclovir) on the risk of birth defects.[64] Although the study reported that only 4 percent of pregnant persons exposed to an antiviral agent during the first trimester had a history of anogenital herpes, there are few reasons (e.g., Bell's palsy) to treat pregnant persons with these medications unless they are experiencing a herpes outbreak. Because the dataset did not capture diagnoses from primary care settings, it is likely that most persons treated with an antiviral agent in this study population were not asymptomatic by our definition. Nonetheless, this study did not find an association between antiviral exposure and major birth defects (adjusted prevalence odds ratio, 0.89 [95% CI, 0.65 to 1.22]).

Ongoing Studies

We identified one ongoing study that would meet our eligibility criteria (KQ 6), the Valacyclovir Treatment of Alzheimer's Disease Trial (NCT03282916; planned N=130), an ongoing randomized trial comparing valacyclovir with placebo. Participants have mild Alzheimer's disease and must test positive for HSV-1 or HSV-2 antibodies. The trial is intended to evaluate whether antiviral treatment with valacyclovir can improve cognition and daily functioning—the primary outcomes—as an anti-Alzheimer's disease drug, but the trial will also collect data on adverse events, which would fall within this review's scope. The estimated primary completion date is August 2022.

Future Directions

We identified two studies that investigated the effect of early HSV treatment during pregnancy to prevent adverse obstetric outcomes such as premature, prolonged rupture of membranes, preterm delivery, and low birth weight.[65, 66] Future iterations of this report could consider a causal pathway in pregnancy that included intermediate obstetric outcomes, as well as health outcomes such as neonatal mortality and morbidity, in addition to harms associated with cesarean section to prevent neonatal HSV transmission.

Conclusions

We found no new evidence since the 2016 USPSTF recommendation against serologic screening for genital herpes in asymptomatic adolescents and adults (D recommendation). Foundational evidence for the prior recommendation against screening is based on psychological harms associated with false-positive test results due to poor screening test accuracy, especially in populations with low HSV-2 prevalence, and uncertain benefit of preventive viral medications for reducing viral shedding or improving health outcomes. We found no new evidence pertaining to pregnant persons.

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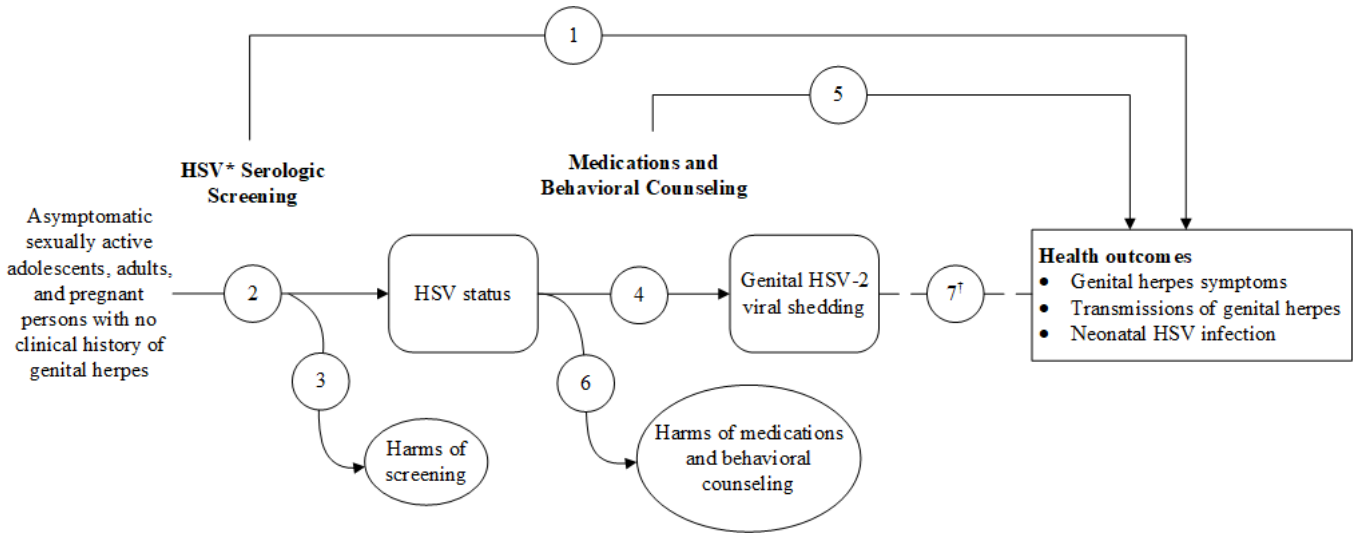
Figure 1. Analytic Framework



* Studies that screened using an HSV-2 serologic test alone or a type-specific serologic test for both HSV-1 and HSV-2 simultaneously were included if they met other eligibility criteria; however, only the accuracy of test characteristics related to HSV-2 serological tests was evaluated.

† KQ 7 will only be addressed if there is insufficient literature for KQs 1 and 5 but sufficient literature for KQ 4.

Abbreviations: HSV=herpes simplex virus; KQ=key question.

Figure 2. Summary of Evidence Search and Selection

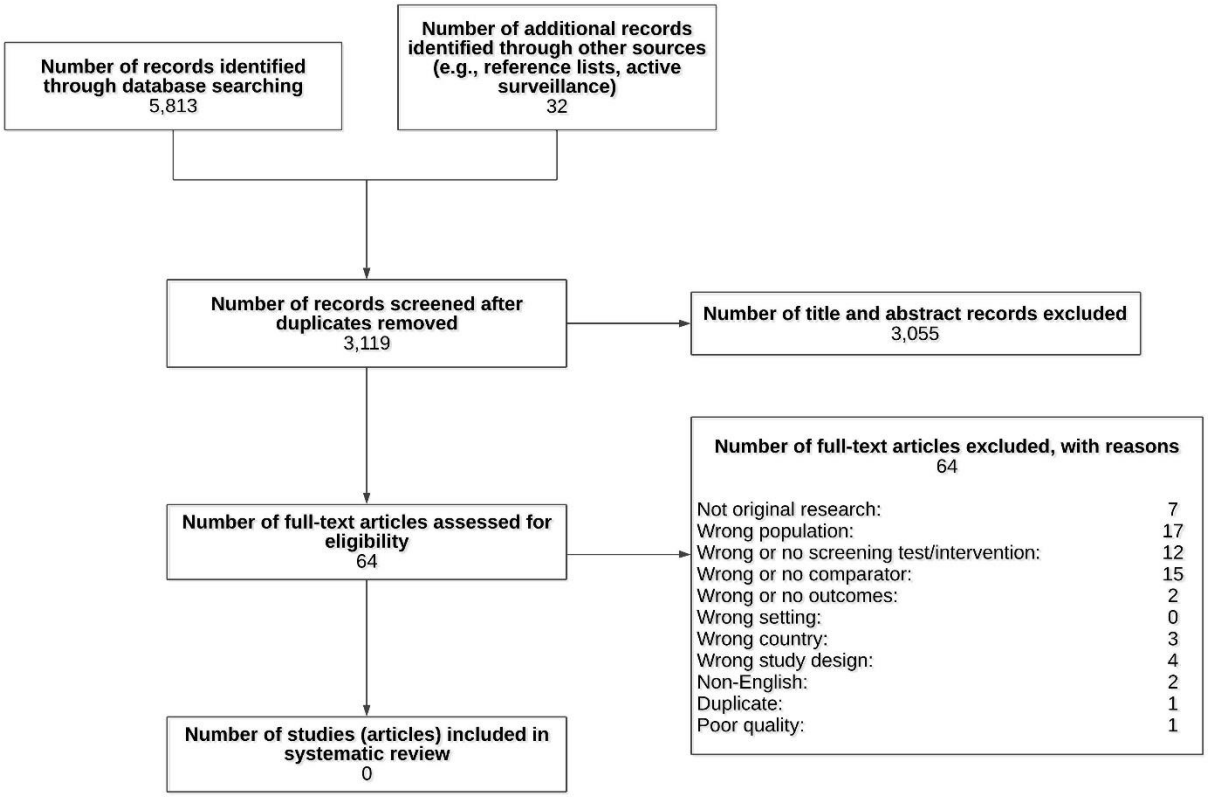


Table 1. Clinical Categories of Genital HSV Infection[62]

Category	Definition	Clinical Manifestations
Primary genital HSV infection	Newly acquired genital HSV infection (either HSV-1 or HSV-2); no serum antibody is present when symptoms appear	Painful genital ulcers or vesicular lesions, potentially associated with dysuria, fever, tender local inguinal lymphadenopathy, and headache; can be subclinical or entirely asymptomatic
Nonprimary genital HSV infection	Newly acquired genital infection with HSV-2 (or HSV-1) in an individual previously seropositive to the other subtype; type-specific antibody to one subtype is initially present while antibody to the new infection may take weeks or months to appear	In general, manifestations tend to be milder than those of primary infection (e.g., fewer lesions and less systemic symptoms); can be subclinical or entirely asymptomatic
Recurrent genital HSV infection	Reactivation of genital HSV in which the HSV type recovered from a lesion is the same type as antibodies in the serum; can be the first clinical episode in people with prior asymptomatic (or unrecognized) genital HSV infection	Ulcerative or vesicular lesions sometimes associated with a prodrome of local itching, tingling, or pain; usually milder and shorter in duration than primary infection; can be subclinical or entirely asymptomatic
Asymptomatic genital HSV infection	Genital HSV infection in which serum antibody is present, but there is no known history of clinical outbreaks	None or potentially mild or unrecognized symptoms previously attributed to another cause

Abbreviation: HSV=herpes simplex virus.

Table 2. Summary of Recommendations for HSV-2 Screening and Management

Organization, Year Country(ies)	Pregnant or Nonpregnant Women?	Recommendation
CDC, 2021[51] U.S.	Both	Screening: 1. Screening for HSV-1 and HSV-2 in the general population is not indicated. 2. Asymptomatic screening using type-specific serologic assays may be useful in persons whose partner has genital herpes. 3. Patients who are at higher risk for infection (e.g., those presenting for an STI evaluation, especially for persons with ≥10 lifetime sex partners, and persons with HIV infection) might need to be assessed for a history of genital herpes symptoms, followed by type-specific HSV serologic assays to diagnose genital herpes for those with genital symptoms. Management: 1. Antiviral therapy is recommended for all persons with a first episode of symptomatic genital herpes. 2. Episodic treatment may be used to treat recurrent outbreaks. 3. Suppressive therapy may be used to reduce recurrent symptomatic outbreaks and to reduce the risk for transmission to susceptible partners in those with a known history of symptomatic HSV infection. Pregnancy (Screening and Management): 1. Routine serologic screening of pregnant women is not recommended. 2. All pregnant women should be asked whether they have a history of genital herpes or genital symptoms raising concern about HSV infection. 3. Type-specific serologic screening may be useful to identify pregnant women at risk for primary HSV infection among women with no personal history of genital herpes whose sex partner has HSV infection. 4. At the onset of labor, all women should be questioned about symptoms of genital herpes and examined for herpetic lesions. 5. Women without known genital herpes should be counseled to abstain from vaginal intercourse during the third trimester with partners known or suspected of having genital herpes. Additionally, women without known orofacial herpes should be advised to abstain from receptive oral sex during the third trimester with partners with known or suspected orofacial herpes. 6. Suppressive antiviral therapy beginning at 36 weeks' gestation is indicated for women with recurrent genital herpes. 7. Women with active genital lesions at the onset of labor should deliver by cesarean delivery.
SOGC, 2017[46] Canada	Nonpregnant	Screening: 1. Routine or targeted HSV screening is not recommended. Management: 1. Suppressive therapy is indicated for patients who have: a. ≥6 recurrences per year b. Significant complications c. Significant effects on their quality of life d. Social and sexual dysfunction e. To lower the risk of transmission to a sexual partner or fetus/neonate

Table 2. Summary of Recommendations for HSV-2 Screening and Management

Organization, Year Country(ies)	Pregnant or Nonpregnant Women?	Recommendation
SOGC, 2017[47] Canada	Pregnant	Screening: 1. Women's history of genital herpes should be evaluated early in pregnancy. 2. Pregnant women who do not have a history of HSV but have a partner with genital HSV should have type-specific testing to determine her risk of acquiring genital HSV. Testing should be performed prior to conception or early in pregnancy and repeated at 32 to 34 weeks' gestation. Management: 1. Women with prodromal symptoms or with active lesions suggestive of HSV at the time of delivery should be offered cesarean section. 2. Women with primary genital herpes in the third trimester should be offered cesarean section. 3. Women with known recurrent genital HSV infection should be offered suppressive therapy starting at 36 weeks' gestation.
BASHH/RCOG, 2014[48] U.K.	Pregnant	Screening: No recommendation for routine or targeted screening. Management: 1. Suppressive antiviral therapy beginning at 36 weeks' gestation should be used for women with symptomatic genital herpes (first episode or recurrent) at any point during pregnancy. 2. Women with a first known episode (primary or nonprimary) of genital herpes during pregnancy should receive acute treatment with acyclovir. 3. Women with active genital lesions due to recurrent infection at the time of delivery should be counseled on the risk of neonatal transmission, and the final choice as to vaginal or cesarean delivery should be made by the mother. 4. Women with a first known episode (primary or nonprimary) of genital herpes during the third trimester should undergo cesarean delivery, particularly within 6 weeks of expected delivery. If vaginal delivery is pursued, intravenous acyclovir should be administered intrapartum. 5. Type-specific serologic testing is indicated for a first known episode of genital herpes in the third trimester to determine if this actually represents a recurrent infection.
ACOG, 2020[45] U.S.	Pregnant	Screening: 1. Routine screening of pregnant women is not recommended. Management: 1. Suppressive antiviral therapy beginning at 36 weeks' gestation is indicated for women with a clinical history of genital herpes. 2. Women with active genital lesions or prodromal symptoms at the onset of labor should deliver by cesarean delivery. 3. Women with primary or first-episode nonprimary infection during the third trimester may be offered cesarean delivery.

Table 2. Summary of Recommendations for HSV-2 Screening and Management

Organization, Year Country(ies)	Pregnant or Nonpregnant Women?	Recommendation
CNGOF, 2018[50] France	Pregnant	Screening: 1. There is insufficient evidence to justify a routine screening policy during pregnancy. Management: 1. For serodiscordant couples in which the mother does not have a history of herpes infection, condom use can be recommended during the third trimester in the absence of clinical lesions. When a lesion is present, sexual relations, including orogenital, should be avoided, especially close to term. 2. Type-specific serologic testing should be used for women with a first episode of genital herpes to differentiate between a primary, nonprimary, or recurrent infection in which the first episode went unnoticed. 3. Antiviral treatment is recommended for a first episode of genital herpes during pregnancy. 4. Suppressive antiviral therapy is recommended starting at 36 weeks of gestation for women with a symptomatic episode of genital herpes (first episode or recurrent) occurring at any time during pregnancy. 5. Cesarean delivery is recommended for women with active lesions from a first episode of genital herpes at the time of delivery or when delivery occurs within 6 weeks of the first episode. 6. For women with recurrent genital herpes and an active genital lesion or prodromal symptoms at the time of delivery, the literature does not justify recommending one type of delivery over another except in cases where the membranes remain intact or there are associated risk factors (i.e., HIV or preterm delivery) when cesarean delivery is recommended.

Table 2. Summary of Recommendations for HSV-2 Screening and Management

Organization, Year Country(ies)	Pregnant or Nonpregnant Women?	Recommendation
Patel et al., 2017 (IUSTI)[49] Europe	Both	Screening: 1. Serologic testing is not routinely recommended in asymptomatic patients. 2. Serologic screening may be useful in sexual partners of patients with genital herpes where concerns are raised about transmission. Management: 1. Antiviral therapy is recommended for all patients with a first episode of symptomatic genital herpes. 2. Patients with recurrent genital herpes may benefit from supportive therapy alone, episodic treatment with antivirals, or with suppressive antiviral therapy with management decisions made in partnership with the patient. Pregnancy (Screening and Management): 1. Routine serologic screening of pregnant women is not recommended. 2. Type-specific serologic screening should be routinely recommended for asymptomatic pregnant women whose partner has a history of genital herpes. 3. All women should undergo careful vulval inspection at the onset of labor to assess for clinical signs of herpes infection. 4. Women without a history of genital herpes who are seronegative for HSV-1 or HSV-2 should be counseled about strategies to prevent a new infection during pregnancy, including selective or complete abstinence (especially during the third trimester) and conscientious condom use. 5. Suppressive antiviral therapy beginning at 36 weeks' gestation may reduce the need for cesarean delivery for women with a history of recurrent genital herpes or women with a first episode of genital herpes occurring at any time during pregnancy. 6. Cesarean section may be considered for women with recurrent active genital herpes lesions at the onset of labor, but the risk of neonatal transmission should be weighed against the risks to the mother of cesarean delivery. 7. Cesarean section should be considered for women with a first episode (primary or nonprimary) of genital herpes during the third trimester, particularly if occurring within 6 weeks of delivery. For women with a first episode during the first or second trimester, vaginal delivery should be anticipated.
AAFP, 2016[44] U.S.	Both	Same as the 2016 USPSTF recommendation. Asymptomatic adolescents and adults, including those who are pregnant, should not receive routine serological screening for genital HSV.
WHO, 2016[67] Global	Treatment	Treatment is recommended over no treatment for adults and adolescents with a first clinical episode of genital HSV infection, including people living with HIV, who are immunocompromised, with a severe episode, and pregnant women. For adults and adolescents with a recurrent clinical episode of genital HSV infection, treatment is recommended within the first 24 hours of symptom onset or during the prodromal phase. This also applies to people living with HIV, who are immunocompromised, and pregnant women. For adults and adolescents with recurrent clinical episodes of genital HSV infection that are frequent, are severe, or cause distress, suppressive therapy is recommended over episodic therapy with reassessment after 1 year.

Abbreviations: AAFP=American Academy of Family Physicians; ACOG=American College of Obstetrics and Gynecology; BASHH=British Association for Sexual Health and HIV; CDC=Centers for Disease Control and Prevention; CNGOF=French College of Gynaecologists and Obstetricians; HIV=human immunodeficiency virus; HSV=herpes simplex virus; IUSTI=International Union Against Sexually Transmitted Infections; RCOG=Royal College of Obstetricians and Gynaecologists; SOGC=Society of Obstetricians and Gynaecologists of Canada; STI=sexually transmitted infection; USPSTF=United States Preventive Services Task Force; WHO=World Health Organization.

Table 3. Summary of Previous 2016 USPSTF Review and New Evidence Identified in This Review

Question Addressed	Rationale and Foundational Evidence	Limitations of Foundational Evidence	New Evidence Findings
Benefits of serologic screening	No direct evidence.	NA	No new evidence.
Accuracy of serologic screening tests	Pooled results from 10 cross-sectional studies (N=6,537) found that the HerpeSelect test with a cut point of 1.1 had a sensitivity of 99% (95% CI, 97% to 100%) and a specificity of 81% (95% CI, 68% to 90%).[68-77] Similarly, pooled results from 7 cross-sectional studies (N=5,516) found that the HerpeSelect test with a cut point of 2.2 to 3.5 had a sensitivity of 95% (95% CI, 91% to 97%) and specificity of 89% (95% CI, 82% to 93%).[68-71, 74-76] Pooled results from 4 cross-sectional studies (N=1,512) found that the Biokit HSV-2 test had a sensitivity of 84% (95% CI, 73% to 91%) and a specificity of 95% (95% CI, 93% to 97%).[71, 73, 75, 77]	Most studies excluded equivocal test results from calculations of sensitivity/specificity (or did not describe the handling of missing data). Their sampling strategy was often not adequately described. Applicability to asymptomatic populations receiving care in U.S. primary care settings was limited. Studies enrolled populations from African countries that have a high prevalence of HSV-2 infection (>50%).	No new evidence.
Harms of serologic screening	Two studies (N=57), a qualitative study and a cohort study, reported on potential harms of screening.[78, 79] The qualitative study (n=24) found that a new HSV-2 diagnosis is associated with 1) short-term, emotional responses (e.g., distress, sadness); 2) short-term, psychological responses (e.g., fear of telling sex partners); and 3) perceived ongoing responses (e.g., feeling sexually undesirable).[78] The cohort study (n=33) found that certain individual items were frequently reported as interfering in daily life on the herpes health-related quality of life (HRQOL) questionnaire: “It is difficult to forget I have herpes” (63%), “I worry about giving herpes to someone” (56%), “I worry about people finding out I have herpes” (48%), and others.[79]	Studies were uncontrolled (i.e., no concurrent control group of people who were not screened). Because of the study design and outcome measures, it was impossible to estimate a magnitude of effect or assess precision.	No new evidence.

Table 3. Summary of Previous 2016 USPSTF Review and New Evidence Identified in This Review

Question Addressed	Rationale and Foundational Evidence	Limitations of Foundational Evidence	New Evidence Findings
Benefits of antiviral medications for reducing viral shedding	Two crossover RCTs (N=129) evaluated the efficacy of valacyclovir or famciclovir for reducing days with any subclinical genital HSV-2 viral shedding detected over 6–8 weeks:[80, 81] • Valacyclovir 1 g daily vs. placebo (n=73): 1.5% vs. 5.1%, respectively; p<0.001[80] • Famciclovir 250 mg twice daily vs. placebo (n=66): 5.7% vs. 5.0%, respectively; RR, 0.8 (95% CI, 0.41 to 1.56); p=0.52[81]	Studies assessed different medications over a short duration. Sample sizes were small, and overall attrition was >20% in both trials.	No new evidence.
Benefits of antiviral medications and behavioral counseling for reducing future symptomatic episodes and transmission	Two crossover RCTs (N=129) evaluated the efficacy of valacyclovir or famciclovir for reducing the incidence of self-reported genital herpes symptoms at 6–8 weeks:[80, 81] • Valacyclovir 1 g daily vs. placebo (n=73): 12% vs. 23%, respectively; p=0.033[80] • Famciclovir 250 mg twice daily vs. placebo (n=66): 17.5% vs. 17.2%; respectively; p-value NR[81] Among serodiscordant couples, 2 parallel RCTs (N=2,421 couples) also evaluated the efficacy of valacyclovir or famciclovir for reducing the incidence of HSV-2 seroconversion over longer-term followup:[30, 82, 83] • Valacyclovir 1 g daily vs. placebo at 32 weeks (n=1,484 couples): benefit in favor of valacyclovir (HR, 0.52 [95% CI, 0.27 to 0.99]; p=0.04)[30, 82] • Acyclovir 250 mg twice daily vs. placebo at 78 weeks (n=937 couples): no difference between groups (HR, 1.35 [95% CI, 0.83 to 2.20]; p=0.220)[83]	For evidence about asymptomatic adults generally, incidence was self-reported, outcomes were measured over a relatively short duration, samples sizes were small, and overall attrition was >20% in both trials. For evidence about serodiscordant couples, the two available studies assessed different medications over different durations in populations that were heterogeneous.	No new evidence.
Harms of antiviral medications and behavioral counseling for reducing future symptomatic episodes and transmission	One parallel RCT (N=63) comparing valacyclovir with placebo found a similar incidence of self-reported adverse events between groups (headache, nausea).[81]	It was unclear if adverse events were prespecified.	No new evidence.
Association between subclinical viral shedding and health outcomes	No evidence.	NA	No new evidence.

Abbreviations: CI=confidence interval; HR=hazard ratio; HRQOL=health-related quality of life; HSV-2=herpes simplex virus-2; KQ=key question; n=number of participants in a study; N=number of participants across studies; NA=not applicable; NR=not reported; RCT=randomized, controlled trial; RR=relative risk; vs.=versus.

CQ 1. What Proportion of Asymptomatic Adolescents, Adults, and Pregnant Persons Who Are Identified as Being Seropositive for HSV-2, HSV-1, or Both Will Have a Recognized Symptomatic Episode of Genital Herpes?

Evidence addressing CQ 1 is summarized in **Appendix A Table 1**. The previous evidence review identified six studies addressing CQ 1, finding that a wide range, from 16 to 87 percent, of asymptomatic individuals seropositive for HSV-2 subsequently developed signs or symptoms of genital herpes.[27, 80, 81, 84-86] Differences between studies in the duration of followup (maximum 5 months) and the methods used to measure symptom occurrence were thought to contribute to the observed heterogeneity in rates. In the current review, we identified two additional secondary analyses of herpes vaccine trials relevant to this question. Overall, those two studies reported values at the lower end of the range (15% and 38%); both studies had longer followup periods compared with the prior studies.

In one study (N=2,393 participants), 98 participants (4.1%) (from either study arm) experienced asymptomatic HSV-2 seroconversion. Eighty-five of those 98 participants (86.7%) were followed for at least 45 days after their first positive HSV-2 serologic test (median 351 days).[87] Of those, 15 percent (13/85) subsequently developed genital lesions at some later time during followup.

The other study followed women seronegative for both HSV-1 and HSV-2 at enrollment who were randomized to the control arm (n=3,438 participants).[10] Asymptomatic seroconversion, defined as seroconversion to either HSV-1 or HSV-2 without presenting with any signs or symptoms of disease within the previous 6 months, occurred in 183 participants (3.7%) over the 20-month followup period. Of the participants who experienced asymptomatic seroconversion, approximately two thirds (n=127) had HSV-1 seroconversion, and one third (n=56) had HSV-2 seroconversion. Overall, 27 percent (49/183) of participants with asymptomatic seroconversion developed genital symptoms. Among those with HSV-1, 22 percent (28/127) developed genital symptoms, while 38 percent (21/56) of those with HSV-2 developed symptoms. This was a study of herpes vaccination, so the self-selected volunteers may have included a group with higher risk for acquiring HSV infection, leading to an overestimate of infection rates compared with the general population.

CQ 2. Are Externally Validated, Reliable Risk Stratification Tools Available That Distinguish Persons Who Are More or Less Likely to Have Genital Herpes?

Similar to the previous review, we identified no externally validated, reliable risk stratification tools to identify individuals more or less likely to have genital herpes.

Appendix A Table 1. Incidence of Symptomatic Episodes Among Asymptomatic Persons Identified as Seropositive for HSV-1, HSV-2, or Both

Source	Author, Year Study Design Country	Population (N)	Ascertainment of Herpes-Related Symptoms and HSV-2 Infection Followup Duration	Proportion With Incident Genital Herpes Symptoms (N)
Previous review	Langenberg, 1989[84] Cohort U.S.	Women recruited from an urban city-county hospital and gynecology clinic who were identified as HSV-2 seropositive but reported no history of genital herpes (62)	Self-report; Western blot 5 months	52% (32) developed symptomatic genital herpes
Previous review	Leone, 2007[80] RCT U.S.	Men and women identified as HSV-2 seropositive who reported no prior history of genital herpes enrolled in a trial assessing viral shedding (66)	Self-report; Western blot 42 days	17.2% (11 during placebo treatment); 17.5% (12 during antiviral medication treatment)
Previous review	Frenkel, 1993[85] Cohort U.S.	Pregnant women recruited from three private obstetrics practices (264)	Self-report; Western blot NR (followed until delivery)	16%* (63)
Previous review	Tronstein, 2011[86] Cohort U.S.	Adult men and women study participants from the University of Washington Virology Research Clinic† (88)	Self-report; Western blot Median: 57 days (IQR, 47–62 days)	68% (95% CI, 58 to 78) (60)
Previous review	Sperling, 2008[81] RCT U.S.	Adult men and women from 13 centers in the U.S. (various clinical settings) identified as HSV-2 seropositive who reported no current or past symptoms consistent with genital herpes enrolled in a trial assessing viral shedding (56)	Self-report; HerpeSelect ELISA (index values 1.1 to 3.5 confirmed with HSV-2 IgG inhibition assay) 2 months	23% (13 overall)
Previous review	Wald, 2000[27] Cohort U.S.	Adults seropositive for HSV-2 with no history of genital herpes, recruited from either 1) a primary care clinic or 2) participants evaluated for entry in an HSV-2 vaccine trial unexpectedly found to be HSV-2 positive‡ (53)	Self-report; Western blot 3 months	87% (46) reported having either genital lesions or localized genital symptoms during followup
Current review	Langenberg, 1999[87] Secondary analysis of 2 RCTs U.S.	Adults initially seronegative for HSV-2 and HIV who experienced asymptomatic HSV-2 seroconversion and were then followed ≥45 days after their first positive HSV-2 serologic test, recruited from 40 clinics into two similarly designed HSV-2 vaccine trials§,‖ (85)	Self-report; Western blot Median: 351 days (IQR, 223–510 days)	15% (13)
Current review	Bernstein, 2013[10] Secondary analysis of RCT Canada and U.S.	Adult women seronegative for both HSV-1 and HSV-2 and randomized to vaccine control arm in an HSV-2 vaccine trial who experienced asymptomatic seroconversion to HSV-1 or HSV-2 (183)	Self-report; HerpeSelect-2 ELISA, followed by Western blot for samples testing positive Range: 20 months	27% (49)

* 56% (N=24) of women recognized HSV lesions during the third trimester; 16 women had their babies by cesarean delivery because of genital herpes.

† Participants were enrolled in prospective studies of the natural history of genital HSV infection.

‡ All subjects attended an individual standardized educational session on genital herpes that included reviewing photographs of herpetic lesions. Photographs of both typical lesions (e.g., blisters and genital herpes ulcers) and atypical lesions (e.g., fissures) were shown, and the common symptoms (e.g., itching and tingling) were discussed.

§ One trial was conducted at 18 centers and enrolled 531 HSV-2 seronegative persons reporting that they had been in an exclusive sexual relationship with a partner infected with HSV-2 for at least 6 months. The second trial was conducted at 22 clinics for the treatment of sexually transmitted diseases and enrolled 1,862 persons who reported having had four or more sexual partners in

Appendix A Table 1. Incidence of Symptomatic Episodes Among Asymptomatic Persons Identified as Seropositive for HSV-1, HSV-2, or Both

the year before enrollment or who reported having one or more of the following sexually transmitted diseases: pelvic inflammatory disease (in women), a first episode of nongonococcal urethritis (in men), gonorrhea, chlamydia, primary or secondary syphilis, or trichomoniasis.

[l] All subjects received standardized counseling about practicing safe sex at every scheduled study visit, including the recommendation to use condoms during each sexual exposure. They were also instructed about the signs and symptoms of genital herpes and were asked to present to the study clinic for evaluation of all genitourinary and orofacial signs and symptoms during the trial.

Abbreviations: CI=confidence interval; ELISA=enzyme-linked immunosorbent assay; HIV=human immunodeficiency virus; HSV=herpes simplex virus; IgG=immunoglobulin G; IQR=interquartile range; N=number; NR=not reported; RCT=randomized, controlled trial.

Appendix B1. Original Search Strategies

PubMed, 7/6/2021

Total Unduplicated Yield = 1,693

Search for KQs 1, 3-7

Search	Query	Filters	Items Found
1	"Herpes Genitalis"[Mesh] OR "genital herpes simplex" OR "Herpesvirus 2, Human"[Mesh] OR "HSV-2"[All Fields] OR HSV2[All Fields] OR Simplexvirus[Mesh] OR "genital herpes"[tiab] OR "Herpes Simplex"[Mesh:NoExp]		41,949
2	"Polymerase Chain Reaction/methods"[Mesh] OR "Immunoenzyme Techniques"[Mesh] OR "Immunoassay/methods"[Mesh] OR "Antibodies, Viral/analysis"[Mesh] OR "Antibodies, Viral/blood"[Mesh] OR "Enzyme-Linked Immunosorbent Assay/methods"[Mesh] OR ("Viral Envelope Proteins"[Majr] AND diagnos*[tw]) OR "Viral Envelope Proteins/analysis"[Majr] OR "Viral Envelope Proteins/immunology"[Majr] OR "Serologic Tests/methods"[Majr] OR "Serologic Tests/standards"[Majr] OR "DNA, Viral/analysis"[Majr] OR "Reagent Kits, Diagnostic"[Majr] OR screen*[tw] OR "Western blot"[tw] OR HerpeSelect[tw] OR "BioKitHSV-2"[tw]		1,417,188
3	#1 AND #2		6,421
4	"Herpes Simplex/diagnosis"[Majr] OR "Herpes Simplex/virology"[Mesh] OR "Herpesvirus 2, Human/immunology"[Majr] OR "Herpes Genitalis/diagnosis"[Majr] OR "Simplexvirus/immunology"[Majr] OR "Herpes Genitalis/virology"[Majr] OR (herpes*[tiab] AND 2*[tiab] AND diagnos*[tiab])		13,014
5	#1 AND #4		9,948
6	"adverse effects" [Subheading] OR "Drug-Related Side Effects and Adverse Reactions"[Mesh] OR "Long Term Adverse Effects"[Mesh] OR "Patient Harm"[Mesh] OR harm OR harms OR "adverse effect*" OR "adverse event*" OR "adverse outcome*" OR complication* OR death OR mortality OR (psychosocial AND test*) OR (emotional AND test*) OR (emotional AND impact) OR (diagnosis AND psychosocial) OR (screen* AND psychosocial) OR (test* AND impact) OR "Social Stigma"[Mesh] OR stigma[tiab] OR labeling[tiab] OR "Anxiety/etiology"[Majr] OR Stereotyping[Mesh]		7,134,893
7	#1 AND #6		10,639
8	"Virus Shedding"[Mesh] OR "viral shedding"[All Fields] OR "virus shedding"[All Fields] OR "Disease Transmission, Infectious"[Mesh]		80,853
9	#1 AND #8		1,092
10	acyclovir OR famciclovir OR valacyclovir OR "Antiviral Agents"[Mesh:NoExp] OR "Antiviral Agents "[Pharmacological Action] OR "suppressive treatment"[tiab] OR "suppressive therapy"[tiab] OR "suppressive agent*"[tiab] OR "suppressive drug*"[tiab] OR "antiviral drug*"[tiab] OR therapy[tiab] OR "antiviral treatment"[tiab] OR "antiviral agent*"[tiab]		2,349,183
11	#1 AND #10		14,160
12	"Patient Education as Topic"[Mesh] OR "Patient Education Handout" [Publication Type] OR "patient education"[All Fields] OR Counseling[Mesh] OR "Secondary Prevention"[Mesh] OR "Disclosure"[Mesh] OR disclosure[All Fields] OR "Contact Tracing"[Mesh] OR "partner notification"[All Fields] OR "Contraception, Barrier"[Mesh] OR "barrier protection" OR "Condoms"[Mesh] OR "Condoms, Female"[Mesh] OR condom*		385,692
13	#1 AND #12		792
14	#3 OR #5 OR #7 OR #9 OR #11 OR #13		28,311
15	#3 OR #5 OR #7 OR #9 OR #11 OR #13	Adult: 19+ years	7,989

Appendix B1. Original Search Strategies

Search	Query	Filters	Items Found
16	#3 OR #5 OR #7 OR #9 OR #11 OR #13	Adolescent: 13-18 years, Adult: 19+ years	8,460
17	#14 AND (Adolescent[Mesh] OR adolescen*[tw] OR Adult[MeSH] OR adult*[tw] OR elderly[tw] OR "middle age"[tw] OR "middle aged"[tw] OR teen[tw] OR teens[tw] OR teenage*[tw])		8,921
18	#14 NOT (boys[tw] OR "Child"[Mesh] OR child[tw] OR children*[tw] OR childhood[tw] OR girls[tw] OR Infant[Mesh] OR infant*[tw] OR neonat*[tw] OR newborn*[tw] OR pediatric*[tw] OR paediatric*[tw])		24,097
19	#14 AND ("Pregnant Women"[Mesh] OR "Pregnancy"[Mesh] OR "Pregnancy Complications, Infectious"[Mesh:NoExp] OR "Pregnancy Outcome"[Mesh] OR pregnan*[tw])		2,150
20	#16 OR #17 OR #18 OR #19		26,858
21	#20 AND ("2015/09/30"[Date - Publication] : "3000"[Date - Publication])		2,937
22	#20 AND ("2015/09/30"[Date - Publication] : "3000"[Date - Publication])	English	2,835
23	"retraction"[All Fields] OR "Retracted Publication"[pt] OR Duplicate Publication [pt] OR Erratum[All Fields]		142,712
24	#21 AND #23		1
25	#21 NOT (address[pt] OR "autobiography"[pt] OR "bibliography"[pt] OR "biography"[pt] OR "case control"[tw] OR "case report"[tw] OR "case reports"[tw] OR "case series"[tw] OR "comment"[pt] OR "comment on"[All Fields] OR congress[pt] OR "dictionary"[pt] OR "directory"[pt] OR "editorial"[pt] OR "festschrift"[pt] OR "historical article"[pt] OR "interview"[pt] OR lecture[pt] OR "legal case"[pt] OR "legislation"[pt] OR letter[pt] OR "news"[pt] OR "newspaper article"[pt] OR "patient education handout"[pt] OR "periodical index"[pt] OR ("Animals"[Mesh] NOT "Humans"[Mesh]) OR rats[tw] OR cow[tw] OR cows[tw] OR chicken[tw] OR chickens[tw] OR horse[tw] OR horses[tw] OR mice[tw] OR mouse[tw] OR bovine[tw] OR sheep OR ovine OR murine OR murinae)		1,557
26	#25 AND ("Systematic Review"[pt] OR ("review"[Publication Type] AND "systematic"[tiab]) OR "systematic review"[All Fields] OR ("review literature as topic"[MeSH] AND "systematic"[tiab]) OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "Systematic Reviews as Topic"[Mesh] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab] OR "meta-synthesis"[tiab] OR "meta-syntheses"[tiab] OR "Umbrella Review"[tiab])		53
27	#25 AND ("randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR randomized [tiab] OR placebo[tiab] OR "drug therapy"[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab])		445
28	#25 AND ("Case-Control Studies"[MeSH] OR "Cohort Studies"[MeSH] OR "comparative study"[pt] OR "Epidemiologic Studies"[MeSH] OR "Cross-Over Studies"[MeSH] OR "Follow-Up Studies"[MeSH] OR "observational study" OR "observational studies" OR "cohort"[tw] OR "case control"[tw] OR "comparative study"[pt] OR "risk factors"[mesh] OR "compared"[tw] OR "groups"[tw] OR "case control"[tw] OR "multivariate"[tw])		632
29	#25 NOT (#26 OR #27 OR #28)		700

Appendix B1. Original Search Strategies

Search for KQ 2

Search	Query	Filters	Items Found
1	"Herpes Genitalis"[Mesh] OR "genital herpes simplex" OR "Herpesvirus 2, Human"[Mesh] OR "HSV-2"[All Fields] OR HSV2[All Fields] OR Simplexvirus[Mesh] OR "genital herpes"[tiab] OR "Herpes Simplex"[Mesh:NoExp]		41,952
2	"Clinical Laboratory Techniques"[MeSH] OR "Diagnostic Test Approval"[MeSH] OR "Diagnostic Tests, Routine"[MeSH] OR "False Negative Reactions"[MeSH] OR "False Positive Reactions"[MeSH] OR "Mass Screening"[MeSH] OR "Predictive Value of Tests"[Mesh] OR "Reproducibility of Results"[Mesh] OR "Risk Assessment"[MeSH] OR "ROC Curve"[Mesh] OR "Sensitivity and Specificity"[Mesh] OR accuracy[tw] OR "false negative"[tw] OR "false positive"[tw] OR "likelihood ratio"[tw] OR "predictive value"[tw] OR reproducib*[tw] OR ROC[tw] OR screen*[tiab] OR sensitivity[tw] OR specificity[tw] OR test*[tiab]		7,980,113
3	#1 AND #2		15,836
4	#1 AND #2	Adult: 19+ years	3,599
5	#1 AND #2	Adolescent: 13-18 years, Adult: 19+ years	3,780
6	#3 AND (Adolescent[Mesh] OR adolescen*[tw] OR Adult[MeSH] OR adult*[tw] OR elderly[tw] OR "middle age"[tw] OR "middle aged"[tw] OR teen[tw] OR teens[tw] OR teenage*[tw])		4,060
7	#3 NOT (boys[tw] OR "Child"[Mesh] OR child[tw] OR children*[tw] OR childhood[tw] OR girls[tw] OR Infant[Mesh] OR infant*[tw] OR neonat*[tw] OR newborn*[tw] OR pediatric*[tw] OR paediatric*[tw])		14,052
8	#3 AND ("Pregnant Women"[Mesh] OR "Pregnancy"[Mesh] OR "Pregnancy Complications, Infectious"[Mesh:NoExp] OR "Pregnancy Outcome"[Mesh] OR pregnan*[tw])		871
9	#5 OR #6 OR #7 OR #8		15,261
10	#9 AND ("2015/09/30"[Date - Publication] : "3000"[Date - Publication])		1,348
11	#9 AND ("2015/09/30"[Date - Publication] : "3000"[Date - Publication])	English	1,313
12	#11 NOT (address[pt] OR "autobiography"[pt] OR "bibliography"[pt] OR "biography"[pt] OR "case control"[tw] OR "case report"[tw] OR "case reports"[tw] OR "case series"[tw] OR "comment"[pt] OR "comment on"[All Fields] OR congress[pt] OR "dictionary"[pt] OR "directory"[pt] OR "editorial"[pt] OR "festschrift"[pt] OR "historical article"[pt] OR "interview"[pt] OR lecture[pt] OR "legal case"[pt] OR "legislation"[pt] OR letter[pt] OR "news"[pt] OR "newspaper article"[pt] OR "patient education handout"[pt] OR "periodical index"[pt] OR ("Animals"[Mesh] NOT "Humans"[Mesh]) OR rats[tw] OR cow[tw] OR cows[tw] OR chicken[tw] OR chickens[tw] OR horse[tw] OR horses[tw] OR mice[tw] OR mouse[tw] OR bovine[tw] OR sheep OR ovine OR murine OR murinae)		784
13	#12 AND ("Systematic Review"[pt] OR ("review"[Publication Type] AND "systematic"[tiab]) OR "systematic review"[All Fields] OR ("review literature as topic"[MeSH] AND "systematic"[tiab]) OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "Systematic Reviews as Topic"[Mesh] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab] OR "meta-synthesis"[tiab] OR "meta-syntheses"[tiab] OR "Umbrella Review"[tiab])		22
14	#12 AND ("randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR randomized [tiab] OR placebo[tiab] OR "drug therapy"[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab])		178
15	#12 AND ("Case-Control Studies"[MeSH] OR "Cohort Studies"[MeSH] OR "comparative study"[pt] OR "Epidemiologic Studies"[MeSH] OR "Cross-Over Studies"[MeSH] OR "Follow-Up Studies"[MeSH] OR "observational study" OR "observational studies" OR "cohort"[tw] OR "case control"[tw] OR "comparative study"[pt] OR "risk factors"[mesh] OR "compared"[tw] OR "groups"[tw] OR "case control"[tw] OR "multivariate"[tw])		393
16	#12 NOT (#13 OR #14 OR #15)		331

Appendix B1. Original Search Strategies

Cochrane Library, 7/6/2021

Total Unduplicated Yield = 95

Search for KQs 1, 3-7

ID	Search	Items Found
#1	[mh "Herpes Genitalis"] OR "genital herpes simplex" OR [mh "Herpesvirus 2, Human"] OR "HSV-2" OR HSV2 OR [mh Simplexvirus] OR "genital herpes" OR [mh ^"Herpes Simplex"]	1206
#2	[mh "Polymerase Chain Reaction"] OR [mh "Immunoenzyme Techniques"] OR [mh Immunoassay] OR [mh "Antibodies, Viral"] OR [mh "Antibodies, Viral"] OR [mh "Enzyme-Linked Immunosorbent Assay"] OR ([mh "Viral Envelope Proteins" [mj]] AND diagnos*:ti,ab,kw) OR [mh "Viral Envelope Proteins"] OR [mh "Serologic Tests" [mj]] OR [mh "DNA, Viral" [mj]] OR [mh "Reagent Kits, Diagnostic"[mj]] OR screen*:ti,ab,kw OR "Western blot":ti,ab,kw OR HerpeSelect:ti,ab,kw OR BioKitHSV-2:ti,ab,kw	88404
#3	#1 AND #2	177
#4	[mh "Herpes Simplex"/DI] OR [mh "Herpes Simplex"/VI] OR [mh "Herpesvirus 2, Human"/IM] OR [mh "Herpes Genitalis"/DI] OR [mh Simplexvirus/IM] OR [mh "Herpes Genitalis"/VI] OR (herpes*:ti,ab AND 2:ti,ab AND diagnos*:ti,ab)	451
#5	#1 AND #4	217
#6	[mh /AE] OR [mh "Drug-Related Side Effects and Adverse Reactions"] OR [mh "Long Term Adverse Effects"] OR [mh "Patient Harm"] OR harm OR harms OR "adverse effect*" OR "adverse event*" OR "adverse outcome*" OR complication* OR death OR mortality OR (psychosocial AND test*) OR (emotional and test*) OR (emotional AND impact) OR (diagnosis AND psychosocial) OR (screen* AND psychosocial) or (test* AND impact) OR [mh "Social Stigma"] OR stigma OR labeling OR [mh Anxiety/ET] OR [mh Stereotyping]	464705
#7	#1 AND #6	450
#8	[mh "Virus Shedding"] OR "viral shedding" OR "virus shedding" OR [mh "Disease Transmission, Infectious"]	1611
#9	#1 AND #8	180
#10	[mh ^"Antiviral Agents"] OR acyclovir OR "antiviral agents" OR "antiviral agent" OR "antiviral drug" OR "antiviral drugs" OR "antiviral treatment" OR famciclovir OR "suppressive agent" OR "suppressive agents" OR "suppressive drug" OR "suppressive drugs" OR "suppressive therapy" OR "suppressive treatment" OR therapy:ti,ab OR valacyclovir	328932
#11	#1 AND #10	688
#12	[mh "Patient Education as Topic"] OR [mh "Patient Education Handout"] OR "patient education" OR [mh Counseling] OR [mh "Secondary Prevention"] OR [mh Disclosure] OR disclosure OR [mh "Contact Tracing"] OR "partner notification" OR [mh "Contraception, Barrier"] OR "barrier protection" OR [mh Condoms] OR [mh "Condoms, Female"] OR condom*	30102
#13	#1 AND #12	108
#14	#3 OR #5 OR #7 OR #9 OR #11 OR #13	975
#15	#14 AND ([mh adult] OR Adult*:ti,ab,kw OR [mh adolescent] OR Adolescen*:ti,ab,kw OR teen*:ti,ab,kw OR teens:ti,ab,kw OR teenage*:ti,ab,kw)	619
#16	#14 NOT (boys:ti,ab,kw OR [mh child] OR child:ti,ab,kw OR children:ti,ab,kw OR girls:ti,ab,kw OR [mh infant] OR infant*:ti,ab,kw OR pediatric*:ti,ab,kw OR paediatric*:ti,ab,kw)	851
#17	#14 AND ([mh "Pregnant Women"] OR [mh Pregnancy] OR [mh ^"Pregnancy Complications, Infectious"] OR [mh "Pregnancy Outcome"] OR pregnan*:ti,ab)	89
#18	#15 OR #16 OR #17	946
#19	#18 with Cochrane Library publication date Between Sep 2015 and Dec 2021	296

Search for KQ 2

ID	Search	Items Found
#1	[mh "Clinical Laboratory Techniques"] OR [mh "Diagnostic Test Approval"] OR [mh "Diagnostic Tests, Routine"] OR [mh "False Negative Reactions"] OR [mh "False Positive Reactions"] OR [mh "Mass Screening"] OR [mh "Predictive Value of Tests"] OR [mh "Reproducibility of Results"] OR [mh "Risk Assessment"] OR [mh "ROC Curve"] OR [mh "Sensitivity and Specificity"] OR accuracy:ti,ab,kw OR "false negative":ti,ab,kw OR "false positive":ti,ab,kw OR "likelihood ratio":ti,ab,kw OR "predictive value":ti,ab,kw OR reproducib*:ti,ab,kw OR ROC:ti,ab,kw OR screen*:ti,ab,kw OR sensitivity:ti,ab,kw OR specificity:ti,ab,kw OR test*:ti,ab	493941
#2	[mh "Herpes Genitalis"] OR "genital herpes simplex" OR [mh "Herpesvirus 2, Human"] OR "HSV-2" OR HSV2 OR [mh Simplexvirus] OR "genital herpes" OR [mh ^"Herpes Simplex"]	1206

Appendix B1. Original Search Strategies

ID	Search	Items Found
#3	#1 AND #2	391
#4	#3 AND ([mh adult] OR Adult*:ti,ab,kw OR [mh adolescent] OR Adolescen*:ti,ab,kw OR teen*:ti,ab,kw OR teens:ti,ab,kw OR teenage*:ti,ab,kw)	257
#5	#3 NOT (boys:ti,ab,kw OR [mh child] OR child:ti,ab,kw OR children:ti,ab,kw OR girls:ti,ab,kw OR [mh infant] OR infant*:ti,ab,kw OR pediatric*:ti,ab,kw OR paediatric*:ti,ab,kw)	333
#6	#3 AND ([mh "Pregnant Women"] OR [mh Pregnancy] OR [mh ^"Pregnancy Complications, Infectious"] OR [mh "Pregnancy Outcome"] OR pregnan*:ti,ab)	52
#7	#4 OR #5 OR #6	381
#8	#7 with Cochrane Library publication date Between Sep 2015 and Dec 2021	147

Embase, 7/6/2021

Total Unduplicated Yield = 907

Search for KQs 1, 3-7

ID	Search	Items Found
#1	'genital herpes'/exp OR 'genital herpes simplex' OR 'herpes simplex virus 2'/exp OR 'hsv-2' OR hsv2 OR 'simplexvirus'/exp OR 'genital herpes' OR 'herpes simplex'/de	70,865
#2	'polymerase chain reaction'/exp OR 'enzyme immunoassay'/exp OR 'immunoassay'/exp OR 'virus antibody'/exp OR 'serology'/exp OR 'enzyme linked immunosorbent assay'/exp OR 'virus envelope protein'/exp OR 'serology'/exp/mj OR 'virus dna'/exp OR 'diagnostic kit'/exp OR screen* OR 'western blot' OR herpeselect OR 'biokithsv-2'	3,366,220
#3	#1 AND #2	20,920
#4	('herpes simplex'/exp/mj/dm_di OR ('herpes simplex'/exp/mj AND virology)) AND 'herpes simplex virus 2'/exp/mj AND immunology OR 'genital herpes'/exp/mj/dm_di OR ('simplexvirus'/exp/mj AND immunology) OR ('genital herpes'/exp/mj AND virology) OR (herpes*:ti,ab AND 2:ti,ab AND diagnos*:ti,ab)	11,951
#5	#1 AND #4	8,197
#6	'adverse drug reaction'/exp OR 'patient harm'/exp OR harm OR harms OR 'adverse effect*' OR 'adverse event*' OR 'adverse outcome*' OR complication* OR death OR mortality OR (psychosocial AND test*) OR (emotional AND test*) OR (emotional AND impact) OR (diagnosis AND psychosocial) OR (screen* AND psychosocial) OR (test* AND impact) OR 'social stigma'/exp OR 'stigma':ab,ti OR 'labeling':ab,ti OR 'anxiety'/exp/mj/dm_et OR 'stereotyping'/exp	6,853,065
#7	#1 AND #6	16,316
#8	'virus shedding'/exp OR 'viral shedding' OR 'virus shedding' OR 'disease transmission'/exp	222,979
#9	#1 AND #8	4,214
#10	acyclovir OR famciclovir OR valacyclovir OR 'antivirus agent'/de OR 'suppressive treatment':ab,ti OR 'suppressive therapy':ab,ti OR (suppressive:ti,ab AND agent*:ab,ti) OR (suppressive:ti,ab AND drug*:ab,ti) OR (antiviral:ti,ab AND drug*:ab,ti) OR therapy:ab,ti OR 'antiviral treatment':ab,ti OR (antiviral:ti,ab AND agent*:ab,ti)	2,944,820
#11	#1 AND #10	20,259
#12	'patient education'/exp OR 'patient education' OR 'counseling'/exp OR 'secondary prevention'/exp OR 'interpersonal communication'/exp OR disclosure OR 'contact examination'/exp OR 'partner notification' OR 'barrier contraception'/exp OR 'barrier protection':ab,ti OR 'condom'/exp OR 'female condom'/exp OR condom*	1,062,833
#13	#1 AND #12	1,941
#14	#3 OR #5 OR #7 OR #9 OR #11 OR #13	47,533
#15	#14 AND ('adult'/exp OR adult*:ti,ab,kw OR 'adolescent'/exp OR adolescen*:ti,ab,kw OR 'middle age':ti,ab,kw OR 'middle aged':ti,ab,kw)	14,352
#16	#14 AND ([adolescent]/lim OR [adult]/lim OR [young adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim)	13,354
#17	#14 AND ('pregnant woman'/exp OR 'pregnancy'/exp OR 'pregnancy complication'/de OR 'pregnancy outcome'/exp OR pregnan*:ti,ab)	2,748
#18	#15 OR #16 OR #17	16,086
#19	#18 NOT ([conference review]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim)	15,165
#20	#19 NOT (([animal cell]/lim OR [animal experiment]/lim OR [animal model]/lim OR [animal tissue]/lim OR 'nonhuman'/exp OR rats OR cow OR cows OR chicken OR chickens OR horse OR horses OR mice OR mouse OR bovine OR sheep OR ovine OR murine OR murinae) NOT 'human'/exp)	14,703

Appendix B1. Original Search Strategies

ID	Search	Items Found
#21	#20 AND [english]/lim	13,280
#22	#21 AND [2015-2021]/py AND [30-9-2015]/sd	4,381
#23	#21 AND [2015-2021]/py AND [30-9-2015]/sd AND ([medline]/lim OR [pubmed-not-medline]/lim)	2,254
#24	#22 NOT #23	2,127
#25	#24 NOT ('autobiography' OR 'bibliography' OR 'biography' OR 'case control' OR 'case report' OR 'case reports' OR 'case series' OR congress OR 'dictionary' OR 'directory' OR 'festschrift' OR 'historical article' OR 'legal case' OR 'legislation' OR 'newspaper article' OR 'patient education handout' OR 'periodical index')	939
#26	#25 AND ('systematic review'/exp OR 'systematic review (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis (topic)'/exp OR 'systematic literature review':ti,ab OR 'this systematic review':ti,ab OR 'umbrella review':ti,ab OR 'meta-analysis':ti,ab OR 'meta-analyses':ti,ab OR 'meta-synthesis':ti,ab OR 'meta-syntheses':ti,ab)	20
#27	#25 AND ('randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'random allocation'/exp OR 'controlled trial'/exp OR 'control trial' OR (('control':ab,ti OR 'controlled':ab,ti) AND 'trial':ab,ti))	506
#28	#25 AND ('case control study'/exp OR 'cohort analysis'/exp OR 'epidemiological study' OR 'crossover procedure'/exp OR 'follow up'/exp OR 'observational study' OR 'observational studies' OR cohort OR 'comparative study'/exp OR 'risk factor'/exp OR compared OR groups OR 'case control' OR multivariate)	555
#29	#25 NOT (#26 OR #27 OR #28)	203

Search for KQ 2

ID	Search	Items Found
#1	'genital herpes'/exp OR 'genital herpes simplex' OR 'herpes simplex virus 2'/exp OR 'hsv-2' OR hsv2 OR 'simplexvirus'/exp OR 'genital herpes' OR 'herpes simplex'/de	70,870
#2	'diagnostic test'/exp OR 'diagnostic test' OR 'diagnostic test approval'/exp OR 'diagnostic test approval' OR 'false negative result'/exp OR 'false negative result' OR 'false positive result'/exp OR 'false positive result' OR 'laboratory technique'/exp OR 'laboratory technique' OR 'mass screening'/exp OR 'mass screening' OR 'predictive value'/exp OR 'predictive value' OR 'reproducibility'/exp OR 'reproducibility' OR 'receiver operating characteristic'/exp OR 'receiver operating characteristic' OR 'risk assessment'/exp OR 'risk assessment' OR 'sensitivity and specificity'/exp OR 'sensitivity and specificity' OR accuracy:ti,ab,kw OR 'false negative':ti,ab,kw OR 'false positive':ti,ab,kw OR 'likelihood ratio':ti,ab,kw OR 'predictive value':ti,ab,kw OR reproducib*:ti,ab,kw OR roc:ti,ab,kw OR screen*:ti,ab,kw OR sensitivity:ti,ab,kw OR specificity:ti,ab,kw OR test*:ti,ab	8,258,103
#3	#1 AND #2	17,412
#4	#3 AND ('adult'/exp OR adult*:ti,ab,kw OR 'adolescent'/exp OR adolescen*:ti,ab,kw OR 'middle age':ti,ab,kw OR 'middle aged':ti,ab,kw)	5,977
#5	#3 AND ([adolescent]/lim OR [adult]/lim OR [young adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim)	5,594
#6	#3 AND ('pregnant woman'/exp OR 'pregnancy'/exp OR 'pregnancy complication'/de OR 'pregnancy outcome'/exp OR pregnan*:ti,ab)	1,208
#7	#4 OR #5 OR #6	6,637
#8	#7 NOT ([conference review]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim)	6,423
#9	#8 NOT (([animal cell]/lim OR [animal experiment]/lim OR [animal model]/lim OR [animal tissue]/lim OR 'nonhuman'/exp OR rats OR cow OR cows OR chicken OR chickens OR horse OR horses OR mice OR mouse OR bovine OR sheep OR ovine OR murine OR murinae) NOT 'human'/exp)	6,192
#10	#9 AND [english]/lim	5,842
#11	#10 AND [2015-2021]/py AND [30-9-2015]/sd	2,162
#12	#11 AND [2015-2021]/py AND [30-9-2015]/sd AND ([medline]/lim OR [pubmed-not-medline]/lim)	1,024
#13	#11 NOT #12	1,138
#14	#13 NOT ('autobiography' OR 'bibliography' OR 'biography' OR 'case control' OR 'case report' OR 'case reports' OR 'case series' OR congress OR 'dictionary' OR 'directory' OR 'festschrift' OR	529

Appendix B1. Original Search Strategies

ID	Search	Items Found
	'historical article' OR 'legal case' OR 'legislation' OR 'newspaper article' OR 'patient education handout' OR 'periodical index')	
#15	#14 AND ('systematic review'/exp OR 'systematic review (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis (topic)'/exp OR 'systematic literature review':ti,ab OR 'this systematic review':ti,ab OR 'umbrella review':ti,ab OR 'meta-analysis':ti,ab OR 'meta-analyses':ti,ab OR 'meta-synthesis':ti,ab OR 'meta-syntheses':ti,ab)	16
#16	#14 AND ('randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'random allocation'/exp OR 'controlled trial'/exp OR 'control trial' OR (('control':ab,ti OR 'controlled':ab,ti) AND 'trial':ab,ti))	286
#17	#14 AND ('case control study'/exp OR 'cohort analysis'/exp OR 'epidemiological study' OR 'crossover procedure'/exp OR 'follow up'/exp OR 'observational study' OR 'observational studies' OR cohort OR 'comparative study'/exp OR 'risk factor'/exp OR compared OR groups OR 'case control' OR multivariate)	334
#18	#14 NOT (#15 OR #16 OR #17)	99

Grey Literature Searches, 7/8/2021

ClinicalTrials.gov Searches

Yield: 1 results, 1 imported

Condition or disease search box:

"Herpes Genitalis" or "genital herpes simplex" or "Herpesvirus 2, Human" or "HSV-2" or HSV2 or Simplexvirus or "genital herpes" or "Herpes Simplex"

Last update posted search box: 03/01/2016 – 07/08/2021

WHO International Clinical Trials Platform

Yield: 75 results, 62 imported

WHO International Clinical Trials Platform Beta Advanced Search (ICTRP Search Portal Advanced Search (ictrptest.azurewebsites.net)) was used because the regular site was inaccessible.

Condition search box:

Herpes Genitalis OR genital herpes simplex OR Herpesvirus 2, Human OR HSV-2 OR HSV2 OR Simplexvirus OR genital herpes OR Herpes Simplex

Recruitment status

Dropdown option: ALL

Date of registration is between: 01/03/2016 and 08/07/2021

Results:

Herpes Genitalis: 6; 6 imported

genital herpes simplex: 4; 4 imported

Herpesvirus 2, Human: 1; 1 imported

HSV-2: 11; 10 imported

HSV2: 0; 0 imported

Simplexvirus: 0; 0 imported

genital herpes: 13; 7 imported

Herpes Simplex: 40; 34 imported

FDA: Drugs@FDA and Devices@FDA

Yield: 5; 5 imported

Drugs@FDA Details

Yield: 4; 4 imported

It was not possible to search Drugs@FDA by topic (i.e., HSV-2), so we initially ran guiding searches with Google and ClinicalTrials.gov to find leads to potentially new drugs and then searched for FDA information about those drugs in Drugs@FDA. For each Google search string, we searched only the first two results pages.

Google Guiding Search Strategy

FDA-approved treatment herpes simplex 2; FDA-approved treatment HSV2; FDA-approved treatment HSV-2; FDA-approved treatment genital herpes; FDA-approved treatment herpes genitalis; FDA-approved treatment herpes virus 2; FDA-approved treatment Simplex virus; FDA-approved treatment herpes simplex

ClinicalTrials.gov Guiding Search Strategy

ClinicalTrials.gov Advanced search for herpes simplex 2, phase III and IV trials, completed only, last update date between March 1, 2016, and July 8, 2021.

Devices@FDA Details

Yield: 1; 1 imported

We also ran guiding searches with Google and ClinicalTrials.gov similar to what was described above for Drugs@FDA to identify any potentially new serologic tests in Devices@FDA.

Google Guiding Search Strategy

serologic* test* herpes simplex 2; serologic* test* HSV2; serologic* test* hsv-2; serologic* test* genital herpes; serologic* test* herpes genitalis; serologic* test* herpesvirus 2; serologic* test* Simplex virus; serologic* test* herpes simplex

ClinicalTrials.gov Guiding Search Strategy

Same as described above for Drugs@FDA.

Appendix B2. Eligibility Criteria

	Include	Exclude
Populations	**All KQs:** Asymptomatic* sexually active adolescents and adults with no clinical history of genital herpes,† including asymptomatic partners of persons with known genital herpes (i.e., discordant couples) and pregnant persons **KQ 2:** Asymptomatic persons or populations unselected based on symptoms or diagnosis of genital herpes **KQs 4–7:** Asymptomatic persons who are HSV-2 seropositive	**All KQs:** Children (younger than age 13 years), persons with HIV infection or other immunosuppressive disorders **KQs 1, 3–7:** Persons with current symptoms (e.g., genital ulcers) or previously diagnosed with genital herpes **KQ 2:** Studies limited to persons with current symptoms of genital herpes or previously diagnosed with genital herpes
Screening	**KQs 1–3:** FDA-approved serologic tests for HSV-2 or type-specific testing for HSV-1 and HSV-2‡	**KQs 1–3:** Serologic tests for HSV-2 that are not commercially available or approved by the FDA; nonserologic tests indicated for the diagnosis of HSV in persons with genital lesions (e.g., cell culture or PCR-based testing); HSV serologic tests that are not type specific
Interventions	**KQs 4–6:** FDA-approved antiviral medications (acyclovir, famciclovir, or valacyclovir) to prevent symptomatic episodes of genital herpes or reduce risk for transmission **KQs 5, 6:** Behavioral counseling interventions, including the following: patient education or counseling, partner notification, barrier protection (e.g., condoms), or combinations of these components; behavioral counseling interventions for seronegative pregnant persons that aim to prevent primary genital HSV infection during pregnancy	**KQs 4–6:** Vaccinations, pharmacotherapy not approved by the FDA for genital herpes **KQs 5, 6:** Routine periodic pelvic examinations to screen for gynecologic conditions (e.g., external inspection for genital ulcers)
Comparisons	**KQ 1:** Screened vs. nonscreened groups **KQ 2:** FDA-approved HSV-2 serologic tests vs. HSV Western blot **KQ 3** (psychosocial outcomes): Any (or no) comparator **KQ 3** (cesarean delivery rate): Screened vs. nonscreened groups **KQs 4–6:** Antiviral medications vs. placebo or no intervention **KQs 5, 6:** Behavioral counseling interventions vs. attention controls or usual care (e.g., provision of a patient handout on genital herpes) **KQ 7:** Higher vs. lower rates (or frequency) of subclinical viral shedding (e.g., percentage of days of subclinical viral shedding)	**KQs 1, 2, 4–7:** No comparison, nonconcordant historical controls, comparative studies of various interventions (e.g., comparing two antiviral drugs or two different type-specific HSV-2 serologic tests)

Appendix B2. Eligibility Criteria

	Include	Exclude
Outcomes	**KQs 1, 5, 7:** Reduced rates of symptomatic genital herpes, reduced rates of genital herpes transmission measured by partner symptom recognition (or clinician diagnosis) or HSV seroconversion, reduced rates of neonatal HSV infection, and reduced rates of symptomatic genital herpes at delivery **KQ 2:** Sensitivity, specificity, positive predictive value, and negative predictive value **KQ 3:** Labeling, anxiety, or false-positive results leading to unnecessary treatment; partner discord, or distress or anxiety related to the meaning of HSV-1 results when screening involves a "paired test" (HSV-1 and HSV-2 results reported together) or other psychosocial harms; and increased rates of cesarean delivery (in persons with no evidence of active genital lesions at the time of delivery) **KQ 4:** Reduced rates (or frequency) of subclinical HSV-2 viral shedding **KQ 6:** Treatment-related adverse events (e.g., adverse drug reactions related to antiviral medications); psychosocial harms related to counseling or behavioral interventions	**All KQs:** Cost-effectiveness or cost-related outcomes, transmission of other sexually transmitted infections (e.g., HIV) **KQ 3:** Acceptability of HSV serologic testing
Study designs	**KQs 1, 4, 5:** RCTs **KQs 2, 3:** Good-quality, recent (within 5 years) systematic reviews[§]; trials or observational studies published since the most recent review **KQ 6:** RCTs and multi-institution antiviral medication pregnancy exposure registries **KQ 7:** Treatment studies included in KQs 4–6 reporting both change in HSV-2 viral shedding and change in a health outcome; prospective cohort studies that follow participants for at least 1 year	All other designs
Setting	**All KQs:** Primary care outpatient settings (or similar settings that are applicable to primary care) **KQs 1, 3–7:** Countries categorized as "Very High" on the Human Development Index, as defined by the United Nations Development Programme **KQ 2:** Any country categorized on the Human Development Index	All other settings
Language	English	Languages other than English
Study quality	Good or fair	Poor (according to design-specific USPSTF criteria)

* "Asymptomatic" refers to persons who have never had clinical symptoms of genital herpes (e.g., genital ulcers), not persons with genital herpes who have symptom-free periods between symptomatic recurrences.
† Eligible studies with mixed populations (e.g., studies that enroll a subset of participants who are seropositive for HSV without a clinical history of genital herpes) were included when results were provided separately or could be obtained from the authors.
‡ Studies that test for both HSV-1 and HSV-2 (simultaneously) were included if they met other eligibility criteria; however, only the accuracy of test characteristics related to HSV-2 serologic tests were evaluated.
§ Previous systematic reviews were included if they were recent (published within 5 years), were of good quality, and were similar in scope to our review. Initial database searches were limited by date of publication for these KQs. If no recent, good-quality systematic reviews were identified, all eligible primary studies that address the KQs were included.

Abbreviations: FDA=U.S. Food and Drug Administration; HIV=human immunodeficiency virus; HSV=herpes simplex virus; KQ=key question; PCR=polymerase chain reaction; RCT=randomized, controlled trial; USPSTF=United States Preventive Services Task Force.

Randomized, Controlled Trials and Cohort Studies

Criteria

- Initial assembly of comparable groups:
  - Randomized, controlled trials (RCTs)—adequate randomization, including first concealment and whether potential confounders were distributed equally among groups
  - Cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, crossovers, adherence, and contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements: Equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- All important outcomes considered
- Analysis: Adjustment for potential confounders for cohort studies or intention-to-treat analysis for RCTs; for cluster RCTs, correction for correlation coefficient

Definition of Ratings Based on Above Criteria

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (followup ≥80%); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention is given to confounders in analysis. In addition, intention-to-treat analysis is used for RCTs.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the important limitations noted in the "poor" category below: Generally comparable groups are assembled initially, but some question remains on whether some (although not major) differences occurred in followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is lacking for RCTs.

Poor: Studies will be graded "poor" if any of the following major limitations exist: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. Intention-to-treat analysis is lacking for RCTs.

Source: U.S. Preventive Services Task Force. U.S. Preventive Services Task Force, Procedure Manual, Appendix VI. Rockville, MD: U.S. Preventive Services Task Force; 2021[58]

Diagnostic Accuracy Studies

Criteria:

- Screening test relevant, available for primary care, adequately described.
- Study used a credible reference standard, performed regardless of test results.
- Reference standard interpreted independently of screening test.
- Handled indeterminate results in a reasonable manner.
- Spectrum of patients included in study.
- Sample size: Although this is one of the criteria listed in the current procedures manual, we did not consider sample size when assessing study quality, because sample size affects precision of the estimate.
- Administration of reliable screening test.

In addition to the criteria listed in the USPSTF procedures manual, we also considered the criteria described in our Appendix D (which details assessments of individual studies).

Definition of Ratings Based on Above Criteria:

Good: Relevant and adequately described study populations for the outcome of interest (i.e., sensitivity, specificity), screening test well described in terms of test procedures followed and threshold used for a "positive" or "negative" test, credible reference standard used for outcome of interest (i.e., sensitivity or specificity), generally interprets reference standard independently of screening test, outcomes clearly reported and valid, handles indeterminate results in a reasonable manner.

Fair: Mostly includes a relevant and adequately described study population for the outcome of interest (i.e., sensitivity, specificity), screening test described although may include some ambiguity about test procedures followed or threshold for a "positive" or "negative" test, credible reference standard mostly used for outcome of interest (i.e., sensitivity or specificity), interpretation of reference standard may or may not be independent of screening test, outcomes mostly clearly reported although may have some ambiguity regarding how indeterminate results were handled.

Poor: Has fatal flaw such as study population not appropriate for outcome of interest (i.e., sensitivity, specificity), screening test improperly administered or not at all described, use of noncredible reference standard, reference and screening test not independently assessed, outcomes not clearly or accurately reported with no information about how indeterminate tests were handled.

Source: U.S. Preventive Services Task Force. U.S. Preventive Services Task Force, Procedure Manual, Appendix VI. Rockville, MD: U.S. Preventive Services Task Force; 2021[58]

Appendix C. Excluded Studies

X1: Not original research
X2: Ineligible population
X3: Ineligible or no screening or treatment
X4: Ineligible or no comparator
X5: Ineligible or no eligible outcome reported
X6: Ineligible setting
X7: Ineligible country
X8: Ineligible study design
X9: Non-English
X10: Duplicate
X11: Poor quality rating

1. Antiviral drugs for varicella-zoster virus and herpes simplex virus infections. *Med Lett Drugs Ther*. 2018 Sep 24;60(1556):153-7. PMID: 30383727. Exclusion Code: X1.
2. Agyemang E, Le QA, Warren T, et al. Performance of commercial enzyme-linked immunoassays for diagnosis of herpes simplex virus-1 and herpes simplex virus-2 infection in a clinical setting. *Sex Transm Dis*. 2017 Dec;44(12):763-7. doi: 10.1097/olq.0000000000000689. PMID: 28876290. Exclusion Code: X11.
3. Agyemang E, Magaret AS, Selke S, et al. Herpes simplex virus shedding rate: surrogate outcome for genital herpes recurrence frequency and lesion rates, and phase 2 clinical trials end point for evaluating efficacy of antivirals. *J Infect Dis*. 2018 Oct 20;218(11):1691-9. doi: 10.1093/infdis/jiy372. PMID: 30020484. Exclusion Code: X8.
4. Agyemang E, Warren T, Selke S, et al. Performance of commercial enzyme-linked immunosorbent assays (ELISAS) for diagnosis of HSV-1 and HSV-2 infection in a clinical setting. *Sex Transm Dis*. 2016;43(10):S220. doi: 10.1097/01.olq.0000503358.65329.6f. Exclusion Code: X1.
5. Anonymous. Erratum: effect of pritelivir compared with valacyclovir on genital HSV-2 shedding in patients with frequent recurrences: a randomized clinical trial (*JAMA*) (2016) 316: 23 (2495-2503)). *JAMA*. 2017;317(6):648. doi: 10.1001/jama.2017.0040. PMID: CN-01335716. Exclusion Code: X2.
6. Ashley Morrow R, Krantz E, Friedrich D, et al. Clinical correlates of index values in the focus HerpeSelect ELISA for antibodies to herpes simplex virus type 2 (HSV-2). *J Clin Virol*. 2006 Jun;36(2):141-5. doi: 10.1016/j.jcv.2006.02.006. PMID: 16677855. Exclusion Code: X2.
7. Atkinson N, Hui L. Antenatal TORCH serology-Time to start choosing wisely? *ANZOG*. 2019;59:88. doi: 10.1111/ajo.13072. Exclusion Code: X1.
8. Atkinson N, Hui L. Antenatal TORCH serology-Time to choose more wisely? *Prenat Diagn*. 2020;40:130-1. doi: 10.1002/pd.5625. Exclusion Code: X1.
9. Binnicker MJ, Espy MJ, Duresko B, et al. Automated processing, extraction and detection of herpes simplex virus types 1 and 2: A comparative evaluation of three commercial platforms using clinical specimens. *J Clin Virol*. 2017 Apr;89:30-3. doi: 10.1016/j.jcv.2017.02.006. PMID: 28226272. Exclusion Code: X3.

10. CEDEF. Item 164 – ue 6 infections à herpès virus du sujet immunocompétent. *Ann Dermatol Venereol*. 2018 Mar;145 Suppl 1:S88-s103. doi: 10.1016/j.annder.2018.01.020. PMID: 29454603. Exclusion Code: X9.
11. Chen L, Liu J, Shi L, et al. Seasonal influence on TORCH infection and analysis of multi-positive samples with indirect immunofluorescence assay. *J Clin Lab Anal*. 2019 May;33(4):e22828. doi: 10.1002/jcla.22828. PMID: 30666721. Exclusion Code: X4.
12. Dargham S, Nasrallah G, Sahara A, et al. Performance of four diagnostic assays for detecting herpes simplex virus type 2 antibodies in middle east and North Africa. *Sex Transm Infect*. 2019;95:A114-. doi: 10.1136/sextrans-2019-sti.288. PMID: CN-01981113. Exclusion Code: X1.
13. Davis A, Roth A, Brand JE, et al. Coping strategies and behavioural changes following a genital herpes diagnosis among an urban sample of underserved Midwestern women. *Int J STD AID*S. 2016 Mar;27(3):207-12. doi: 10.1177/0956462415578955. PMID: 25792549. Exclusion Code: X4.
14. de Ory F, Guisasola ME, Balfagón P, et al. Comparison of commercial methods of immunoblot, ELISA, and chemiluminescent immunoassay for detecting type-specific herpes simplex viruses-1 and -2 IgG. *J Clin Lab Anal*. 2018 Jan;32(1)doi: 10.1002/jcla.22203. PMID: 28332725. Exclusion Code: X4.
15. Euctr DE. Monoclonal antibody therapy against chronic herpes simplex virus 2 infection. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2019-000880-26-DE. 2019PMID: CN-02068592. Exclusion Code: X2.
16. Feltner C, Grodensky C, Ebel C, et al. Serologic screening for genital herpes: an updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2016 Dec 20;316(23):2531-43. doi: 10.1001/jama.2016.17138. PMID: 27997660. Exclusion Code: X8.
17. García-Cisneros S, Sánchez-Alemán M, Conde-Glez CJ, et al. Performance of ELISA and Western blot to detect antibodies against HSV-2 using dried blood spots. *J Infect Public Health*. 2019 Mar-Apr;12(2):224-8. doi: 10.1016/j.jiph.2018.10.007. PMID: 30389368. Exclusion Code: X3.
18. Glaxo Wellcome Inc. Acyclovir Pregnancy Registry. International final study report, 1 Jun 1984 through 30 Apr 1999. Published 1999. Exclusion Code: X2.
19. Gopal R, Gibbs T, Slomka MJ, et al. A monoclonal blocking EIA for herpes simplex virus type 2 antibody: validation for seroepidemiological studies in Africa. *J Virol Methods*. 2000;87(1-2):71-80. Exclusion Code: X3.
20. Govender S, Mbambo L, Nyirenda M, et al. Herpes simplex virus-2 infections in pregnant women from South Africa: Evaluation of the ImmunoFLOW rapid test. *Afr J Lab Med*. 2020;9(1):854. doi: 10.4102/ajlm.v9i1.854. PMID: 32934909. Exclusion Code: X4.
21. Gupta R, Wald A, Krantz E, et al. Valacyclovir and acyclovir for suppression of shedding of herpes simplex virus in the genital tract. *J Infect Dis*. 2004;190(8):1374-81. Exclusion Code: X2.
22. Hallfors DD, Cho H, Mbai, II, et al. Disclosure of HSV-2 serological test results in the context of an adolescent HIV prevention trial in Kenya. *Sex Transm Infect*. 2015;91(6):395-400. doi: 10.1136/sextrans-2015-052025. PMID: CN-01090000. Exclusion Code: X3.

23. Heineman TC, Bernstein D, Wald A, et al. Analysis of a phase 2B study of gen-003, a genital herpes immunotherapy, showed significant reductions in viral shedding and lesion rate vs placebo. *Open Forum Infect Dis*. 2017;4:S59-. doi: 10.1093/ofid/ofxl62.140. PMID: CN-01957933. Exclusion Code: X3.
24. Hobbs MM, Mwanyumba SW, Luseno WK, et al. Evaluation of herpes simplex virus type 2 serological tests for use with dried blood spots in Kenya. *Sex Transm Dis*. 2017 Feb;44(2):101-3. doi: 10.1097/olq.0000000000000557. PMID: 28081046. Exclusion Code: X4.
25. Horn EE, Turkheimer E, Strachan E. Psychological distress, emotional stability, and emotion regulation moderate dynamics of herpes simplex virus type 2 recurrence. *Ann Behav Med*. 2015;49(2):187-98. doi: 10.1007/s12160-014-9640-9. PMID: CN-01113241. Exclusion Code: X2.
26. JapicCTI J. Phase III Study of AK-120 in Patients with Recurrent Herpes Simplex. http://www.who.int/trialsearch/Trial2.aspx?TrialID=JPRN-JapicCTI-163223. 2016PMID: CN-01837848. Exclusion Code: X2.
27. Kang M, Hanson I. STIs in adolescents and young adults prevention and screening. *Med Today*. 2020;21(11):57-62. Exclusion Code: X1.
28. Kawashima M, Kato T, Fujii C, et al. Single-day, patient-initiated Famciclovir treatment for recurrent herpes simplex: a randomized, placebo-controlled, double-blind, parallel-group, multicenter phase 3 study. *JOCD*. 2018;35(3):488-96. doi: 10.3812/jocd.35.488. Exclusion Code: X2.
29. Li D-K, Ferber J, Odouli R, et al. Does treating genital herpes during pregnancy improve birth outcomes? Patient-Centered Outcomes Research Institute (PCORI). 2021. https://doi.org/10.25302/04.2021.CER.151032461 Exclusion Code: X2.
30. Li Z, Yan R, Yan C, et al. Evaluation of an automated chemiluminescent immunoassay in typing detection of IgG antibodies against herpes simplex virus. *J Clin Lab Anal*. 2016 Sep;30(5):577-80. doi: 10.1002/jcla.21905. PMID: 26666528. Exclusion Code: X4.
31. Loughman T, Singh B, Seddon B, et al. Validation of a membrane touch biosensor for the qualitative detection of IgG class antibodies to herpes simplex virus type 2. *Analyst*. 2017 Jul 24;142(15):2725-34. doi: 10.1039/c7an00666g. PMID: 28708188. Exclusion Code: X4.
32. Majewska A, Przybylski M, Machura P, et al. Comparison of three multiplex real-time PCR assays for the detection of herpes simplex viruses type 1 and type 2 DNA. *Med Dosw Mikrobiol*. 2016;68(2):119-25. PMID: 30351744. Exclusion Code: X3.
33. Marić I, Winn VD, Borisenko E, et al. Data-driven queries between medications and spontaneous preterm birth among 2.5 million pregnancies. *Birth Defects Res*. 2019 Oct 1;111(16):1145-53. doi: 10.1002/bdr2.1580. PMID: 31433567. Exclusion Code: X2.
34. McNeil LK, Siddall N, Baccari A, et al. Functional antibody responses to gen-003, a herpes simplex virus immunotherapy that durably reduces viral shedding up to 12 months post dosing. *Open Forum Infect Dis*. 2016;3doi: 10.1093/ofid/ofw172.1046. PMID: CN-01934010. Exclusion Code: X3.
35. Meyers D, Duncan J. Serologic screening for genital herpes infection. *Am Fam Physician*. 2017 Jun 15;95(12):801-2. PMID: 28671417. Exclusion Code: X8.
36. Micks E, Son H, Magaret A, et al. The effect of hormonal contraception and menstrual cycle timing on genital herpes simplex virus-2 shedding and lesions. *Sex Transm Dis*. 2019 Jan;46(1):58-62. doi: 10.1097/olq.0000000000000907. PMID: 30148758. Exclusion Code: X5.

37. Micks EA, Son H, Magaret A, et al. The effect of hormonal contraception on genital herpes simplex virus-2 shedding and lesions. *Contraception*. 2017;96(4):302. doi: 10.1016/j.contraception.2017.07.146. Exclusion Code: X2.
38. Milpied B, Janier M, Timsit J, et al. [Genital herpes]. *Ann Dermatol Venereol*. 2016 Nov;143(11):729-33. doi: 10.1016/j.annder.2016.09.009. PMID: 27771124. Exclusion Code: X9.
39. Money DM, Steben M. No 208-directive clinique sur la prise en charge du virus de l'herpès simplex pendant la grossesse. *J Obstet Gynaecol Can*. 2017 Aug;39(8):e192-e8. doi: 10.1016/j.jogc.2017.04.017. PMID: 28729111. Exclusion Code: X10.
40. Morrow RA, Friedrich D. Inaccuracy of certain commercial enzyme immunoassays in diagnosing genital infections with herpes simplex virus types 1 or 2. *Am J Clin Patho*. 2003;120(6):839-44. Exclusion Code: X2.
41. Morrow RA, Friedrich D, Krantz E. Performance of the focus and Kalon enzyme-linked immunosorbent assays for antibodies to herpes simplex virus type 2 glycoprotein G in culture-documented cases of genital herpes. *J Clin Microbiol*. 2003;41(11):5212-4. Exclusion Code: X2.
42. Munday PE, Vuddamalay J, Slomka MJ, et al. Role of type specific herpes simplex virus serology in the diagnosis and management of genital herpes. *Sex Transm Infect*. 1998;74(3):175-8. Exclusion Code: X4.
43. Nahmias AJ, Josey WE, Naib ZM, et al. Perinatal risk associated with maternal genital herpes simplex virus infection. *Am J Obstet Gynecol*. 1971;110(6):825-37. Exclusion Code: X2.
44. 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. *Reprod Health*. 2017 Mar 3;14(1):31. doi: 10.1186/s12978-017-0292-7. PMID: 28253893. Exclusion Code: X7.
45. Nakubulwa S, Kaye DK, Bwanga F, et al. Incidence and risk factors for herpes simplex virus type 2 seroconversion among pregnant women in Uganda: A prospective study. *J Infect Dev Ctries*. 2016 Oct 31;10(10):1108-15. doi: 10.3855/jidc.6874. PMID: 27801374. Exclusion Code: X4.
46. Narovlyansky AN, Sedov AM, Pronin AV, et al. Treatment of patients with chronic recurrent herpes virus infection of genital localization: a clinical study of fortepren preparation. *Zh Mikrobiol Epidemiol Immunobiol*. 2015. Jul-Aug;4:112-8. PMID: CN-01161697. Exclusion Code: X3.
47. Nascimento MC, Ferreira S, Sabino E, et al. Performance of the HerpeSelect (Focus) and Kalon enzyme-linked immunosorbent assays for detection of antibodies against herpes simplex virus type 2 by use of monoclonal antibody-blocking enzyme immunoassay and clinicovirological reference standards in Brazil. *J Clin Microbiol*. 2007;45(7):2309-11. Exclusion Code: X4.
48. Nasrallah GK, Dargham SR, Sahara AS, et al. Performance of four diagnostic assays for detecting herpes simplex virus type 2 antibodies in the Middle East and North Africa. *J Clin Virol*. 2019 Feb;111:33-8. doi: 10.1016/j.jcv.2019.01.001. PMID: 30639845. Exclusion Code: X4.
49. NCT03080961. The VIBLOK SAfety and perFormancE Trial. 2017. Exclusion Code: X4.
50. NCT04294030. NOWDx test for the diagnosis of herpes simplex virus type 2. 2020. Exclusion Code: X4.

51. Nicholson M, O'Farrell N. Genital herpes - diagnosis, treatments, attitudes and response to disclosure amongst members of the UK Herpes Viruses Association. *Int J STD AIDS*. 2021 Jan;32(1):23-9. doi: 10.1177/0956462420951477. PMID: 33115318. Exclusion Code: X8.
52. Nikolic D, Lesourd S, Slev P, et al. Comparison of the sensitivity of a type-specific and a combined immunoassay against HSV-1 and HSV-2. *Ann Clin Lab Sci*. 2015;45(4):472-3. Exclusion Code: X1.
53. Nowotny KM, Frankeberger J, Rodriguez VE, et al. Behavioral, psychological, gender, and health service correlates to herpes simplex virus type 2 infection among young adult Mexican-American women living in a disadvantaged community. *Behav Med*. 2019 Jan-Mar;45(1):52-61. doi: 10.1080/08964289.2018.1447906. PMID: 29558260. Exclusion Code: X3.
54. Pasternak B, Hviid A. Use of acyclovir, valacyclovir, and famciclovir in the first trimester of pregnancy and the risk of birth defects. *JAMA*. 2010;304(8):859-66. Exclusion Code: X2.
55. Patel EU, Manucci J, Kahle EM, et al. Precision of the Kalon Herpes Simplex Virus Type 2 IgG ELISA: an international inter-laboratory assessment. *BMC Infect Dis*. 2015 Sep 30;15:398. doi: 10.1186/s12879-015-1130-6. PMID: 26423888. Exclusion Code: X3.
56. Patibandla S. Performance evaluation of prototype herpes-I IgG and herpes-II IgG assays∗ on the ADVIA Centaur XP immunoassay system. *Clin Chem*. 2016;62(10):S142. Exclusion Code: X4.
57. Prince HE, Batterman HJ, Schwab DA. Herpes simplex virus type 2 (HSV-2) IgG index values in two immunoassays in relation to HSV-2 IgG inhibition assay results. *Diagn Microbiol Infect Dis*. 2019 Nov;95(3):114864. doi: 10.1016/j.diagmicrobio.2019.07.002. PMID: 31395403. Exclusion Code: X4.
58. Sani AS, Abraham C, Denford S, et al. Are sexual health programmes in sub-Saharan African schools effective in promoting condom use and preventing sexually-transmitted infections including HIV? A systematic review and meta-analysis. *HIV Med*. 2016;17:30. doi: 10.1111/hiv.12393. Exclusion Code: X3.
59. Stone KM, Reiff-Eldridge R, White AD, et al. Pregnancy outcomes following systemic prenatal acyclovir exposure: conclusions from the international acyclovir pregnancy registry, 1984-1999. *Birth Defects Res A Clin Mol Teratol*. 2004;70(4):201-7. Exclusion Code: X2.
60. Virók D, Eszik I, Mosolygó T, et al. A streamlined, quantitative PCR based measurement of herpes simplex virus antiviral susceptibility and herpes simplex virus-specific neutralizing antibodies. *Acta Microbiol Immunol Hung*. 2017;64:95-6. doi: 10.1556/030.64.2017.0.101. Exclusion Code: X3.
61. You Y, Wang L, Li Y, et al. Multicenter randomized study of inosine pranobex versus acyclovir in the treatment of recurrent herpes labialis and recurrent herpes genitalis in Chinese patients. *J Dermatol Sci.* 2015;42(6):596-601. doi: 10.1111/1346-8138.12845. PMID: CN-01084286. Exclusion Code: X2.

Appendix D Table 1. Quality Assessment of Screening Test Accuracy Studies (KQ 2), Part 1

First Author, Year Index Test	Was the cut point used to determine test positivity adequately described (or referenced)?	Were population selection criteria clearly described?	Did the whole or a random selection of the participants receive the Western blot?	Did all participants receive the Western blot regardless of serologic screening test results?	Were the serologic test results and Western blot results interpreted independently?
Agyemang, 2017[60]* Focus HerpeSelect 2	Yes	Yes	No	No	NR/CND

***** Diagnostic test accuracy of the Focus HerpeSelect HSV-2 ELISA (n=98). Reported sensitivity of 100 percent and specificity of 61 percent. These results would not meaningfully alter the pooled sensitivity and specificity previously reported of 99 percent and 81 percent, respectively (10 studies, n=6,537).

Abbreviations: ELISA=enzyme-linked immunosorbent assay; HSV=herpes simplex virus; n=number of participants; KQ=key question; NR/CND=not reported/cannot determine.

Appendix D Table 2. Quality Assessment of Screening Test Accuracy Studies (KQ 2), Part 2

First Author, Year Index Test	What was the overall attrition?	Were withdrawals from the study explained (post-enrollment)?	Were methods for calculating accuracy clearly reported and valid?	Did the study have high attrition raising concern for bias?	What was the method used to handle missing data?	Quality	Comments
Agyemang, 2017[60] Focus HerpeSelect 2	1.0%—1 indeterminate test of 98 overall tests	Yes	Yes	NR/CND	Indeterminate results excluded	Poor	Reference test not performed for all participants. Unclear blinding, but because positive index tests were preferentially sent for reference testing, unlikely that test results were interpreted independently.

Abbreviations: KQ=key question; NR/CND=not reported/cannot determine.

Appendix E Table 1. Ongoing Studies

Study Reference/ Trial Identifier Primary Investigator	Study Name	Location	Estimated N	Target Patient Population	Comparison(s) of Interest	Relevant Outcomes	Status (as of Sep 2021) Projected Completion Date
NCT03282916 Davangere P. Devanand	Antiviral therapy: Valacyclovir Treatment of Alzheimer's Disease (VALAD) Trial	U.S.	130	Adults with mild Alzheimer's disease and testing positive for HSV-1 or HSV-2 antibodies (note that women must have been post-menopausal for ≥12 months)	2-arm RCT comparing 1) valacyclovir and 2) placebo	Adverse events and safety	Recruiting August 2022

Abbreviations: HSV=herpes simplex virus; N=number of participants; RCT=randomized, controlled trial; Sep=September; U.S.=United States.