

Epidemiology

Genital herpes is an infection caused by the herpes simplex virus (HSV) and, for practical purposes, encompasses lesions on the genitals and nearby areas (i.e. buttocks, anal area and thighs). Genital herpes may be due to HSV-1 (the usual cause of orolabial herpes) or HSV-2 (more commonly associated with genital lesions). Although HSV-2 is the most common cause of genital infection, a significant proportion of anogenital herpes is caused by HSV-1.

The epidemiology of genital HSV-2 infection is based on studies of serological evidence of HSV-2, as the majority of HSV-2 infections are genital with comparatively few oral infections. Consistent findings between countries are that HSV-2 seroprevalence increases with:

Age: The incidence of new infections is highest amongst young adults, but as infection is lifelong, overall prevalence increases with increasing age.¹ The Dunedin cohort study found an increasing HSV-2 seroprevalence of 3%, 11% and 18% at ages 21, 26 and 32 years respectively.²⁻⁴

Female gender: Women are more likely than men to be HSV-2 seropositive.¹ The reasons for this are unclear; suggestions include anatomical differences that increase vulnerability to infection or sexual mixing that may expose women to a higher prevalence of infection at a younger age. In 2004-5, at age 32, women in the Dunedin cohort study had an HSV-2 seroprevalence of 22% whilst that in men was 15%.⁴

Like HSV-2, HSV-1 seroprevalence increases with increasing age and tends to be more common in women.

Geographical variation

HSV-2 prevalence varies between countries and seems to be higher in the USA than in Europe, Australia and New Zealand. It also varies depending on the demographics of the population being tested.¹

HSV-1 seroprevalence studies cannot distinguish between oral and genital infection sites which makes it much more difficult to estimate the prevalence of genital HSV-1 infection. Clinical case data has limitations as well. That said, HSV-1 accounts for 35% of confirmed anogenital infections in Australia⁵ and similarly a Waikato-wide study found 30-40% of anogenital isolates are due to HSV-1 each year.⁶ In that study, HSV-1 accounted for 53% of positive isolates from under-25 year olds, 30% in the 25–35 year olds, and 26% from over-35 year olds. Likewise, an Auckland Sexual Health Clinic study in 2004 found most true primary episodes of genital herpes were HSV-1, whilst non-primary first episodes and recurrences were mostly HSV-2.⁷

Note: Routine typing of isolates enhances a clinician's ability to give prognostic information and optimal clinical care. It is no longer accurate to assume that anogenital herpes is due to HSV-2 infection, as a substantial proportion of people will have HSV-1. The natural history of anogenital HSV-1 infection is towards significantly fewer clinically apparent recurrences and much less subclinical shedding.^{8,9} Also, prior HSV-1 infection does not alter the risk of acquisition of HSV-2, although it does attenuate the symptoms; it is important for those diagnosed with HSV-1 anogenital herpes to understand that they remain at risk of HSV-2 infection.

In summary:

As many as one in five adults have genital herpes due to HSV-2, but most will have asymptomatic or unrecognised disease. Genital herpes due to HSV-1 has also become common; HSV-1 is the more frequent cause of primary genital herpes.

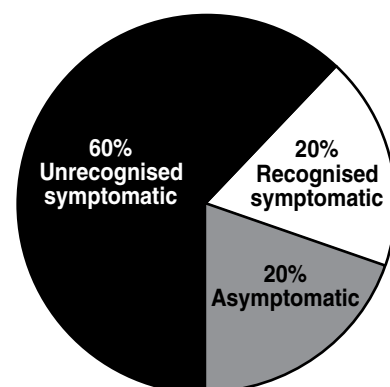


Figure 1: Prevalence, manifestations of genital herpes

Transmission

Herpes simplex virus enters the body, either through a break in the skin or through mucous membranes, during direct contact with infected secretions or mucosal surfaces. For genital infections, this is usually during sexual contact, with HSV-2 commonly transmitted during vaginal or anal sex and HSV-1 commonly passed on through oral-genital sex.

Transmission is most likely to occur:

- During sexual contact
- When the skin is broken
- When there are lesions (e.g. vesicles or ulcers) present
- From men to women

Therefore, sexual contact should be avoided when active lesions are present.

Transmission may occur when a partner is shedding virus asymptomatically. Most people who acquire genital herpes get it from someone who is unaware they are infected, who may have mild or asymptomatic infection.⁹

It is important to remember that, whilst a first clinical episode of genital HSV-1 or HSV-2 may represent a new infection, it may also be a first symptomatic recurrence of a previously asymptomatic or unrecognised infection.

The virus is readily inactivated at room temperature and by drying; hence, non-contact forms of spread, for example via fomites, are considered unlikely. Autoinoculation resulting in spread to different anatomical sites can occur (e.g. orolabial, whitlow), although this is believed to be uncommon. **GRADE C**

Asymptomatic viral shedding

Nearly everyone, both men and women, with genital HSV-2 infection sheds virus from time-to-time without symptoms, which is why sexual transmission can occur during asymptomatic periods. These intermittent episodes of asymptomatic viral shedding are more frequent:

- With genital HSV-2 than genital HSV-1 infection
- During the first 12 months after acquiring HSV-2
- In those with more frequent symptomatic episodes
- Within a week before or after a symptomatic episode
- In those with HIV infection

The viral load threshold for transmission from an episode of asymptomatic shedding has not been established. For a given individual it is impossible to be certain when asymptomatic viral shedding occurs, but it is important not to give the impression that people are infectious all the time.

Reducing Risk of Transmission

Barrier methods

Male and female latex condoms appear impermeable to HSV-2, but in 'real-life' do not give absolute protection for a variety of reasons; condoms do not cover all affected areas, condom breakage or slippage may occur, close genital contact or contact with infectious secretions may occur during foreplay, etc.¹⁰ Nonetheless, consistent condom use offers moderate protection against HSV-2 infection in both men and women.¹¹ **GRADE B.** Data on male condoms preventing transmission to men or on the efficacy of female condoms is lacking. Condom use should be discussed and left to the individual couple's choice.

Oral-genital contact

It is generally believed that prior orolabial HSV-1 infection protects an individual against genital HSV-1. Possible exceptions may be those infected simultaneously at more than one site or those with very recent HSV-1 infection who have not yet seroconverted. People who do not acquire HSV-1 during childhood are at risk of HSV-1 at any site, including genital infection, during adulthood. Transmission may occur whilst receiving oral sex from someone who has oral HSV-1, even if the source partner is asymptomatic. It is estimated that up to a third of persons who are HSV-1 antibody positive do not have a clinical diagnosis of oral herpes,¹² but will still shed HSV-1 virus.¹³

Receptive oral-genital contact should be avoided when oral lesions are present. **GRADE C**

Oral HSV-2 isolation is uncommon. However, oral isolation of HSV-2 has been noted in those with HIV infection and in men who have sex with men, usually at the same time as genital HSV-2 symptoms.¹⁴

Antivirals

Aciclovir, famciclovir and valaciclovir all suppress symptomatic and asymptomatic shedding, by up to 80-95%.¹⁵ Also, it has been shown that suppressive once daily valaciclovir resulted in reduced transmission to the discordant partner.¹⁶ For partners, there was a 48% reduction in acquisition of HSV infection and a 75% reduction in clinical symptomatic genital herpes. Other antivirals may be similarly effective, but this has not been proven in clinical trials.

Co-infection

In most studies, pre-existing HSV-1 infection does not decrease the risk of HSV-2 infection, but prior HSV-1 means HSV-2 infection is more likely to be asymptomatic.¹⁷ If HSV-2 genital infection is acquired first, then a new HSV-1 genital infection does not affect the frequency of recurrences.

In summary:

- Condom use needs to be assessed within the individual situation.
- Using condoms reduces, but does not eliminate, the risk of male to female transmission.
- Sexual contact should be avoided when oral or genital lesions are present.

Diagnostic Tests

Clinical diagnosis alone is insensitive and inaccurate, with a 20% false positive rate.¹⁷ **Suspected genital herpes must be confirmed by appropriate laboratory tests.** Recurrent lesions, which may be atypical, likewise should be tested for HSV. **However, it is important not to delay appropriate therapy while awaiting confirmation.**

Detection of herpes simplex virus in the lesion establishes the diagnosis unambiguously. Viral detection may involve culture, HSV DNA or direct detection of antigen. Vesicles offer the best source of virus. However, as with all laboratory tests, results depend on multiple factors including the adequacy of the specimen. A negative result therefore may not exclude infection. If direct HSV tests are repeatedly negative and the symptoms are recurring, the patient should be advised to have type-specific herpes serology. **GRADE B.**

Culture

HSV isolation in cell culture has been the diagnostic gold standard for many years. Specificity of culture is virtually 100%, but sensitivity is highly dependent on the stage of the clinical lesions, with an isolation rate of over 90% from vesicular or pustular lesions, 70% from ulcerative lesions, but only 27% at the crusting stage.¹⁸ Delayed transport of the specimen to the laboratory may further reduce yield. Positive results are usually reported within 2-5 days, but occasionally may take longer.

PCR

HSV DNA detection by polymerase chain reaction (PCR) increases HSV detection rates compared with virus culture. This is largely because it avoids problems that may affect culture results such as inadequate quantity of specimen, bacterial contamination, and inadvertent inactivation of virus by sub-optimal handling and sample transport delays. Increasingly, PCR is being implemented as the preferred diagnostic method for genital herpes, particularly since the advent of commercially available real-time assays. However, stringent quality control is necessary because of potential contamination by 'carryover' DNA from other biological samples¹⁹ and local validation is recommended.

Direct immunofluorescence

Is no longer recommended as a routine test.

Direct immunofluorescence testing for the viral antigen, present in the cells lining the base of the blister or the ulcerated lesion, shows lower sensitivity and specificity than virus culture. Rapid diagnosis is possible, but it requires operator expertise in obtaining an adequate specimen and a negative result should be interpreted with caution. It is no longer recommended as a routine test.

For patients with active lesions, direct viral detection by either culture or PCR, but not serology, is the recommended diagnostic method.

Sample collection

The following tests have a low false positive rate. However, a negative test result does not necessarily exclude HSV infection since all methods are dependent on adequate collection of the specimen and, for culture in particular, on correct specimen handling and prompt transportation to the laboratory. It is important to be aware of locally available tests so that an appropriate sample is taken. **Viral typing should be requested routinely.**

Culture

- Select appropriate swab; NZ dedicated viral transport swabs (Virocult®) are available. These are usually 'green-topped' and packaged with a sleeve containing a small amount of viral transport medium.
- Swab the lesion firmly. The aim is to collect any vesicular fluid that may be present and to collect virus-infected cells from the base of the lesion.
- Insert swab into plastic tube.
- Place on a cold source, e.g. melting ice or slika pad, and send chilled to the virus laboratory. The swab should arrive the same day since the virus will decay with transport time.

PCR

- Check with local laboratory if HSV PCR is routinely available. If not, may need to specify "for herpes simplex DNA" and offer clinical explanation as to why this is the preferred test over culture, e.g. CSF sample.
- Swab as for viral culture.
- Transport time to the laboratory is less important than with culture.

Serology

Serological tests detect antibodies to HSV in blood and indicate past infection. Type specific tests, based on glycoprotein G (gG) assays, detect antibodies to the type specific proteins gG-1 and gG-2 and detect established infection with HSV-1 and HSV-2. They do not distinguish the anatomical site of infection (see Table 1). Type specific tests are used in population surveys, but their diagnostic reliability in individual patients is still debated. **False negative and false positive results are common in low prevalence populations.** Seroconversion following initial infection is usually 2-6 weeks, but may be longer (months). Also, some do not seroconvert and reversal from seropositive to seronegative status may occur if there is minimal antigenic stimulation. It is a useful test in some clinical situations, but routine screening of asymptomatic individuals is currently not recommended. **GRADE B**

Situations where measurement of type-specific antibody might be helpful include:

- Recurrent or atypical genital symptoms with negative HSV cultures and/or PCR.
- Management of herpes in pregnancy (see page 22).
- Where one partner in a relationship has symptomatic genital herpes. This may be important for discordant couples (a pregnant woman with a symptomatic male partner) as it may be appropriate to counsel abstinence in the last weeks of pregnancy and/or for the male partner to take suppressive antiviral therapy.

The person ordering serology should be able to supply appropriate pre- and post-test counselling.
A positive HSV-2 serology result may cause significant psychological morbidity (see page 12-13).

KEY INFORMATION TO DISCUSS WITH A PATIENT WHO ASKS FOR A BLOOD TEST

- Explain whether the test is for HSV-1 and HSV-2 antibodies or just HSV-2 antibodies. If the blood test being done only tests for HSV-2 antibodies a negative test does not rule out the possibility of the person having genital herpes caused by type 1.
- The window period for antibodies developing following infection is usually 2-6 weeks, but may be longer (months).
- Caution is needed in the interpretation of results. Because false negatives and false positives occur, the results have to be weighed together with the clinical presentation and patient's history.
- Implications for the presence of only HSV-1 antibodies need to be explained. HSV-1 is a common infection, usually acquired in childhood, and may be shed from the oropharynx by asymptomatic individuals. Infection with HSV-1 does not necessarily imply sexual exposure, but genital infection with HSV-1 is increasingly common.

Table 1: Interpreting blood test results

	HSV-2 negative	HSV-2 positive
HSV-1 negative	No antibodies detected*; consider at risk of infection to both types.	No HSV-1 antibodies detected*; consider at risk of infection to HSV-1. HSV-2 antibodies imply prior infection. Does not specify site of infection, but genital infection is more likely with HSV-2.
HSV-1 positive	No HSV-2 antibodies detected*; consider at risk of infection to HSV-2. HSV-1 antibodies imply prior infection, but does not specify site of infection. Genital HSV-1 infection is increasingly common.	HSV-1 and HSV-2 antibodies imply prior infection with both. Does not specify site of infection for HSV-1, but genital infection is more likely with HSV-2.

* May be within window period, may not have seroconverted or may have seroreverted.