

## Serology for Herpes Simplex Virus

### TIPS, PITFALLS AND MISCONCEPTIONS

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Serology is a valuable tool for diagnosing certain sexually transmitted and blood-borne infections (STBBI) and for counselling patients on how to prevent their transmission. Failure to understand how to use it or how to assess its limitations may nevertheless be very risky. Misdiagnosing genital herpes or falsely reassuring patients about the absence of infection may have negative consequences for them, their new sexual partners and their future children.

### Epidemiological Context

A study conducted among pregnant women in British Columbia revealed that the seroprevalence for herpes simplex virus type 1 (HSV-1) was 57 %, while it was 13 % for herpes simplex virus type 2 (HSV-2).<sup>1</sup> Once age-adjusted, the seroprevalence for HSV-2 in the general population was 17 %. It rose from 7.1 % among those aged 15-19 years, to 28.1 % among those aged 40 to 44 years.<sup>1</sup>

According to the 2009 to 2011 Canadian Health Measures Survey, the HSV-2 seroprevalence was 13.6 % among people aged 14 to 59 years,<sup>2</sup> a group consisting of 2.9 million Canadians. Seroprevalence was higher among women (16.1 %) than men (11 %).<sup>2</sup> Moreover, the difference between the sexes was more pronounced among younger people, post-secondary graduates and people whose racial background was reported to be white. The prevalence of HSV-2 was 6.1 % among people aged 14 to 34 years, 19.1 % among those 35 to 49 years of age and 18.9 % among those aged 50 to 59. Only 6 % were aware that they were infected with HSV-2.<sup>2</sup>

Lastly, unlike some US studies, the Canadian study noted no differences by marital status, household income, education or racial background.

## Serology as a Diagnostic Aid: Green Light

### CASE 1

*Roger has had recurrent genital lesions on his penis over the past several years. He is concerned about this and comes to your office, even though he does not currently have active lesions, because he wants to know if you could prescribe an ointment that would help heal his sores faster. Would you prescribe a serological test for herpes simplex virus?*

If someone presents with genital ulcers, the differential diagnosis must include genital herpes, the most common cause of genital ulcerations in the world.<sup>3</sup> An HSV detection test by culture or by nucleic acid amplification technique (NAAT) is then recommended because a positive result confirms genital herpes and the HSV serotype in question.<sup>4</sup>

In the absence of lesions, but when the patient's history is compatible with recurrent genital herpes for more than three months, as in Roger's case, it is acceptable to order HSV type-specific serology. In case of a negative result, it would be prudent to redo the test six months after the onset of signs and symptoms.

Owing to Roger's medical history, the detection time, which may exceed three months for HSV, is not in play. In fact, if he had genital herpes, HSV seroconversion would already have occurred. In case of a negative result for HSV-1 and HSV-2, a diagnosis of genital herpes could be discarded.

In case of a positive result for HSV-2 in someone who has already presented with recurrent genital lesions, a diagnosis of genital herpes is very probable. In fact, the positive predictive value of HSV serology is very high if the result is equal to or greater than 3.5 (compared with a low positive result, from 1.1 to <3.5).<sup>5</sup>

If the serological results show the presence of HSV-1, it is nonetheless impossible to know if the person has orolabial herpes or genital herpes, or both. In general, genital herpes recurrences are much less frequent for HSV-1 than for HSV-2. It bears reminding that positive serological results for HIV, syphilis or hepatitis B or C must be confirmed by other tests in order to increase the

positive predictive value, but this is not possible for HSV in Québec. Neither should it be forgotten that having orolabial herpes does not protect against genital herpes type 1 or 2. The clinical picture will nevertheless be less severe.

HSV serology is a good tool to help establish a presumptive diagnosis of genital herpes. The person must nevertheless see a physician in the case of lesions in order to have a viral identification test performed to confirm the diagnosis.

In the case of an initial episode of genital herpes characterized by general signs and symptoms, bilateral lesions and different types of lesions (blisters, ulcers and crusted sores during the same episode), HSV serology can facilitate the diagnosis if you take into account the seroconversion time of three to six months after the onset of the signs and symptoms of infection and if you compare the result obtained with those of the serum collected at the time of the initial lesions. You would need to write a note on the order asking the laboratory to keep the initial serum for purposes of later comparison. However, this procedure is recommended only when access to the viral identification test is unavailable. This is not an ideal practice.

## HSV Serology as a Screening Test: Red Light

### CASE 2

*Mary has just broken up with a partner who was a fickle lover, to say the least. She is devastated. She is also in a panic because her partner never used a condom with her since their STBBI screening at the start of their relationship nearly two years earlier. Although she has no signs or symptoms, she wants to undergo a complete STBBI screening test, particularly for genital herpes. Would you prescribe a serological screening test for genital herpes?*

Screening is one of the pillars of STBBI prevention and is performed in people without signs or symptoms but with risk factors. Having a single partner who has had multiple partners is one of the STBBI screening criteria, according to the *Guide québécois de dépistage des ITSS*.<sup>6</sup> However, in the absence of a compatible clinical history, HSV serology does not meet the conditions for a good screening test, especially owing to the probability of false positive and the ensuing anxiety, need to make difficult decisions regarding disclosure, potential need for lifelong preventive measures, labelling and, of course, stigma (see box<sup>7</sup>). Moreover, screening is appropriate when an effective test and population acceptance are available and the problem constitutes a serious threat to public health<sup>8</sup>. Also, the ideal screening period is unknown, because the time to seroconversion may exceed three months. Only 73 % of patients with primary HSV-1 infection, 73 % of those with non-primary HSV-2 infection, and 93 % of those with primary HSV-2 infection will obtain positive results with existing serological tests after three months.<sup>9</sup>

### LABELLING AND STIGMATIZATION: DEFINITIONS<sup>5</sup>

**+** Labelling: “Labelling refers to the representations and language used to order the social world, based on values that are considered norms at that time. The social labelling of specific groups of persons may result in their being viewed negatively by the rest of the system’s actors.”

Stigmatization: According to E. Goffman (1963), “Stigmatization is a dynamic process of devaluation that significantly discredits a person in the eyes of others.”

[Translation]

*If you had agreed to prescribe a genital herpes test for Mary, how would you react to the following results?*

- Anti-HSV-1 antibody is 8.7 and anti-HSV-2 is 7.6:
  - Cross-reactivity whereby an elevated titre of antibodies to HSV-1 leads to a false positive for HSV-2?
  - Orolabial HSV-1 infection and genital HSV-2 infection?
- Anti-HSV-1 antibody is 3.6 and anti-HSV-2 is 0.3:
  - Orolabial or genital HSV-1 herpes?
  - Orolabial and genital HSV-1 herpes?
  - Owing to the high prevalence of HSV-1, it is impossible to determine the site of infection in the absence of symptoms. In fact, the result is positive whether the patient has orolabial herpes, simple genital herpes or both.
- Anti-HSV-1 antibody is 0.2 and anti-HSV-2 is 2.7:
  - A false positive or a true low positive for HSV-2?

It is difficult to respond to all of these situations with any certainty. Hypotheses are possible, but not the clear, straightforward and precise answers that our patients like. Table 1<sup>5</sup> provides the interpretation of HSV serological test results.

**Tableau 1 Interpretation of HSV serological test results<sup>5</sup>**

- >1.10 : positive
- From  $\geq 0.90$  to  $< \text{or} = 1.10$  : indeterminate result. Retest the patient. If the result is still indeterminate, retest again by an immunoblot test.
- < 0.90 : negative

The definitive question that recurs in HSV detection is: Which preventive measure would you recommend for each of these cases? Rapid disclosure to the partner, condoms, dental dam, daily valacyclovir, C-section? When you do not know how to react to a positive result, you should not screen because the risks are clearly significantly greater than the benefits. Before ordering a screening test, clinicians should make sure that the harms potentially caused to the person are very low. Clearly, HSV serological testing does not meet that criterion.

### Why is HSV Serology not a good screening test?

There are multiple reasons.

- Detection time is particularly long and can easily exceed three months.
- A positive serological result, especially for HSV-1, does not make it possible to identify the site of HSV infection.
- The sensitivity and especially the specificity of the serological test are less than 100 %, which gives a poor positive predictive value among the populations where the prevalence is low.
- The lack of a confirmation test, like with the other STBBIs detectable by serology (e.g., hepatitis B, hepatitis C, HIV infection and syphilis), makes interpreting the results risky at best.

The positive predictive value, or the probability that a positive result is a true positive, in a population where the prevalence of genital HSV-2 herpes is 5 %, would be 71 %. As a result, 29 % of people at low risk would obtain false positive results.<sup>10</sup> A serological test is always more reliable when the expected prevalence of an infection is high. Consequently, it is not surprising that there are fewer false positives among people with prior lesions than among those without symptoms. Table 2<sup>10</sup> describes the effects of the prevalence of HSV on the performance of HSV type-specific serological tests.

**Tableau 2 Effects of the prevalence of HSV on the performance of HSV type-specific\* serological tests**

	PPV (%)	NPV (%)	False positives (%)	False negatives (%)
5 %	71 %	100 %	29 %	0 %
10 %	83 %	100 %	17 %	0 %
15 %	88 %	99 %	12 %	1 %
20 %	90 %	99 %	10 %	1 %

\* : Assumes test sensitivity of 95 % and specificity of 98 %.

PPV : positive predictive value; NPV: negative predictive value.

Source: Scouler A. Using the evidence base on genital herpes: Optimising the use of diagnostic tests and information provision. *Sex Transm Infect* 2002;78(3):160-5. Reprinted with permission.

The Comité sur les analyses de laboratoire en lien avec les ITSS (CALI) advises against HSV serological testing in the following situations:

- Screening among populations with an increased risk of STBBI, such as men who have sex with men, and people with multiple partners;
- Systematic screening in pregnant women;
- General population screening.

When a test result is to be transmitted to patients in a context of uncertainty and hypothesis, screening should not take place. And that's the end of it!

*It is therefore not recommended to prescribe an HSV serological screening test for Mary.*

## HSV Serology to Prevent Transmission of Infection: Yellow Light

### CASE 3

*Thomas is worried. His new girlfriend has suggested that he should undergo an STBBI screening test and then stop using condoms. He is particularly concerned because for seven years he lived with a partner who had frequent outbreaks of genital HSV-2 herpes confirmed by culture. He has used condoms with his new girlfriend only during the first three months, but has never had any genital herpes lesions. He is afraid that he is an HSV-2 carrier and that he will infect his girlfriend or a future baby.*

*Would you have Thomas undergo genital herpes tests, knowing his history? Most people infected with HSV-2 are unaware that they are infected, and the annual rate of HSV-2 transmission from women to men is 4.5%.<sup>11</sup> Serology is therefore warranted, because the probability that Thomas was infected during those seven years is quite high. If the result were positive, his partner could then be tested to find out if the couple is seroconcordant or serodiscordant in order to choose the best preventive measures before and during pregnancy. But, and there is a “but”, serology could yield a false negative or a false positive. In the event of a positive result, his partner should still be tested, even though there is also a risk for her of a false-positive or false-negative result.*

*Given that most cases of neonatal herpes in Canada are caused by HSV-1, it is prudent to tell pregnant women to avoid sexual contact with their partner’s mouth during pregnancy and even more so during the third trimester. In this particular case, however, if Thomas were seropositive for HSV-1, this advice would apply even if you did not know if he had orolabial herpes, genital herpes, or both.*

*If Thomas were seropositive for HSV-2, you could prescribe daily valacyclovir, recommend that he use condoms even during the pregnancy and tell him to see a doctor for confirmation by a viral test in case of lesions.<sup>12</sup> However, treatment with valacyclovir would not be recommended for HSV-1.*

## Conclusion

HSV serology can facilitate the diagnosis of herpes in individuals presenting with recurrent lesions. However, HSV-2 screening in an asymptomatic person can cause harm because of false positives and because a positive HSV-1 screening test does not indicate the site of infection. HSV serology can help serodiscordant couples choose the necessary and appropriate methods before or after pregnancy to prevent transmission of HSV.

### KEY POINTS

**+** HSV serology must be prescribed to facilitate diagnosis or to choose preventive measures if in case of the probability of serodiscordance in a couple, but not for screening.

Interpreting HSV serology results can prove to be complex and may require help from an experienced colleague.

HSV serology yields too many false-positive and false-negative rates to make it a good screening test, and there is no test to confirm positive results.

## To learn more

For a general review of the transmission of genital herpes:

Steben M, Sénéchal K. Prévenir la transmission de l’herpès génital : une question de négociation! *Le Médecin du Québec* 2006;41(2):63-7.

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## AUTHORS

### AUTEURS

Marc Steben, Medical Advisor  
Direction des risques biologiques et de la santé au travail  
l'Institut national de santé publique du Québec and

Medical Director  
Clinique A rue McGill au sein du GMF l'Actuel

Gabrielle Landry, Family Physician  
Clinique A rue McGill et Clinique médicale l'Actuel

Rachel Cruz de Menezes, Nurse  
Centre de santé et de services sociaux du Centre-Sud-de-l'île-de-Montréal.

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