

**EVALUATION OF SCREENING FOR ASYMPTOMATIC HERPES SIMPLEX
VIRUS TYPE 2 INFECTION
AGAINST NSC HANDBOOK CRITERIA
2005-01-25**

| Criteria | Evidence |
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| <u>The condition</u> | |
| <p>1. The condition should be an important health problem</p> | <p>Herpes virus type 2 is the cause of genital herpes, which manifests itself by recurring painful vesicular lesions in and around the genital area. The majority of the infections, however, go without symptoms. It is a sexually transmitted disease which could also be transmitted from mother to child during delivery.</p> <p>Virus can be isolated from the visible lesions, but diagnosis of genital herpes is usually made by inspection and medical history. The only practical way to identify infected people with otherwise unrecognised genital herpes is by serological tests.</p> <p>The occurrence of the infection, as measured by serological markers, differs between groups of people, geographical areas and over time. In the general population of UK, as indicated by two serological studies from the 1990s, the occurrence should be less than ten percent.</p> <p>It is an important <i>reproductive</i> health problem. For those with symptoms it is often a stigmatized condition. Obstetric and paediatric staff must relate to the condition and risks for the newborn child.</p> <p>Neonatal herpes is a serious consequence of genital herpes virus infection. The risk of transmission in and around delivery is less than one percent in women with long-standing infection, but it is said to be substantially higher, if the maternal infection is acquired during late pregnancy. Untreated herpes infection has among the highest mortality of any infection in the neonatal period and neurological afflictions are common among the survivors. The risk for neonatal herpes is very low in communities with low seroprevalence of herpes virus type 2 infection. The serological status of the mother is not a reliable indicator of whether neonatal herpes is going to occur or not.</p> |

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| | <p>Currently there is no treatment available to eliminate the infection except the provision of information, counselling, psychosocial support, and antiviral suppressive therapy.</p> |
| <p>2.</p> <p>i) The epidemiology of the condition should be known</p> <p>ii) The natural history of the condition should be understood</p> <p>iii) There should be a recognised latent period or early symptomatic stage</p> | <p>The occurrence and the dynamics of genital herpes infection in the general population are not well known. We know that the spread is by sexual intercourse or from mother to child during delivery. Once infected one remains a carrier of the infection for a very long time, probably for a life-time. The level of contagiousness fluctuates and seems to decline with time.</p> <p>We do not know enough of how the epidemiology and natural history of the condition relates to other sexually transmitted diseases and to the other common herpes virus infection of type 1 to make informed decisions.</p> <p>There is no well defined latent period or early symptomatic stage for infection with herpes virus type 2.</p> |
| <p>3. All cost effective primary prevention interventions should have been implemented as far as practicable</p> | <p>A cost effective primary prevention should ideally be by vaccination of the population before child-bearing age. As yet no such vaccine exists for public use.</p> <p>In promotion of reproductive health and in sexual education genital herpes should be on the agenda. Sexual education of young people could be likened to vaccinations; for effectiveness it has to be delivered in a proper way to each birth cohort with almost 100 percent coverage followed by repeated booster doses.</p> <p>Proper and timely primary prevention interventions have evidently not been implemented in an efficacious way as can be judged by available sexual and reproductive health indicators.</p> |

| <u>The test</u> | |
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| 4. There should be a simple, safe, precise and validated screening test | <p>Commercial serology tests in kit forms have become available in the past few years for herpes virus type 1 and type 2 infections. They are fairly simple technically. Precision will depend on who is performing the test; spread on too many hands, the precision will probably be lower than when the examinations are centralised. Validation is difficult since no real gold standard exists in the form of a reliable diagnostic test of whether a person carries virus or not. A simple, safe, precise and validated screening test does not exist.</p> <p>Type specific commercial tests generally have values of sensitivity and specificity ranging around 95 percent. Sensitivity of the commercial tests is usually more variable across kits than is specificity. The more commonly used tests could be verified by an assay with maximal specificity, e.g. western blot. The western blot assay is expensive, labour intensive and unlikely to become widely available.</p> <p>Predictive values depend on the sensitivity and specificity of a test and, most importantly, on the occurrence of the disease in the groups being tested. The positive predictive value of a test may be very low, if the prevalence is low, even with a high sensitivity and a high specificity. The wide variation in sero-prevalence of herpes virus type 2 infection makes prevalence important for the application of a test, even if its sensitivity and specificity are on an accepted level. In low-prevalence populations 30-40 percent of the tested individuals will wrongly be diagnosed as being infected; even in high-prevalence groups like attendants in an STD clinic, around 10 percent are at risk of getting a false diagnosis. Likewise, a proportion will wrongly be labelled as non-infected, which especially does not help when one is dealing with neonatal herpes.</p> |
| 5. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed | The distribution of the infection is not known in the general population and therefore suitable cut-off levels for the serological tests could not be defined and agreed upon. |
| 6. The test should be acceptable to the population | We do not know if the test is acceptable to the population; some people would like to know, others not. For those with symptoms it might be a relief to understand what they are afflicted by. For others it might just be a life-long stigma. |

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| | <p>The partners' situation is also complicated. What are their rights to decide whether to be tested or not? Can their autonomy be violated by the source patient exerting pressure as part of a partner notification program? Can their rights be violated even if they don't know? The testing can be of help in confirming a diagnosis suspected on clinical grounds. An asymptomatic partner, however, will have the same problem as the index patient in understanding all the implications of the outcome of sero-testing.</p> |
| <p>7. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test and on the choices available to those individuals</p> | <p>In scientific studies the western blot test – another serological test – is used as verification. This test is however cumbersome and expensive and not suitable for use in extensive screening procedures.</p> <p>An agreed policy on further diagnostic investigations of individuals with a positive test has yet to be decided upon.</p> <p>Agreed policies exist for how to care for pregnant women with symptomatic genital herpes and their offspring. Screening of asymptomatic pregnant women and their partners is fraught with interpretation problems and complicated by deliberations on probabilities for something to occur, on which the scientific community in no way is unanimous. Since the risk for neonatal herpes is very low in communities with low sero-prevalence of herpes type 2 infection and the serological status of the mother is not a reliable indicator of whether neonatal herpes is going to occur or not, the ethical costs of antenatal screening is high and the clinical benefits doubtful.</p> |
| <p><u>The treatment</u></p> | |
| <p>8. There should be an effective treatment or intervention for patients identified through early detection</p> | <p>Suppressive therapy exists, given early in the natural course of the manifest disease it is said to relieve pain and shorten the attacks.</p> <p>The benefits of suppressive therapy on asymptomatic infections are not well known. There are indications that treatment lessen the risk for transmission.</p> |
| <p>9. There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered</p> | <p>There is no evidence based knowledge and consensus on how to treat sero-positive individuals without symptoms, bearing also in mind that the infection and its contagiousness fluctuate over time.</p> <p>People with symptoms benefit from antiviral treatment in that their attacks seem to become shorter and they have less pain.</p> |

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| | <p>Concern for herpes virus type 2 transmission to infants is likely to result in administration of antiviral drugs to the mother or in a Caesarean delivery.</p> |
| <p>10. Clinical management of the condition and patient outcomes should be optimised by all health care providers prior to participation in a screening programme</p> | <p>Reasonable societal support need to be available and affordable for those labelled as infected by herpes virus type 2 as well as their partners.</p> <p>The medical staff should be prepared to respect patient autonomy and honour the difficulties in sharing the intricate bio-epidemiology, which is special for herpes type 2 infection, with their patients. This will be time-consuming.</p> <p>There are no justice costs for the patients if the patients are offered the test independently of social or economic status and are informed in a way that respects the individual variation in understanding and preparedness to internalize and act on the information. Within a high risk population appeals to solidarity as a requirement for diminishing the transmission and thereby the suffering would be a possible strategy. But the average citizen does not contact an STD clinic. Due to the intricacies of understanding the problems and implications with the tests, equity might be jeopardized if some patients only have access to health care staffed with professionals from other specialities outside STD clinics.</p> |
| <p><u><i>The screening programme</i></u></p> | |
| <p>11. There should be evidence from high quality Randomised Controlled Trials that screening programme is effective in reducing mortality or morbidity</p> | <p>Evidence from high quality Randomised Controlled Trials that a screening programme for herpes virus type 2 infection is effective in reducing transmission does not exist.</p> |
| <p>12. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is clinically, socially, and ethically acceptable to health professionals and the public</p> | <p>Valid and contextualised evidence whether a complete screening programme is clinically and socially acceptable to the public does not exist.</p> <p>There is an ongoing scientific discussion on how far to extend testing for herpes virus type 2 infection and for which groups, mostly with arguments from a biomedical perspective. The scientific community is visibly divided on the issue with screening proponents mainly coming from the United States. The issue of cost-effectiveness has also been brought forward. Conclusive evidence is not at hand.</p> |

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| <p>13. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment)</p> | <p>A screening programme ideally aims at eradicate the virus. Realistically, this would not be possible in a foreseeable future and the aims would instead be to lessen the transmission. For the policy level and the general public the benefits of a low prevalence of genital herpes is obvious. If this is the same as a low sero-prevalence of herpes virus infection type 2 is another matter. A primary infection during late pregnancy is associated with a high risk for viral exposure of the infant and a possible caesarean section. If the primary infections were experienced in age groups before pregnancy takes place, the risk for transmission to newborns would lessen.</p> <p>The benefit from a herpes type 2 screening programme does not outweigh the potential psychological harm due to the still often unclear implications with the tests for the index cases and their partners.</p> <p>Screening of pregnant women may increase the likelihood for unnecessary Caesarean delivery and physical harm for both the mother and the newborn child.</p> |
| <p>14. The opportunity costs of the screening programme (including testing, diagnosis and treatment) should be economically balanced in relation to expenditure on medical care as a whole</p> | <p>The opportunity costs of a complete screening programme for asymptomatic herpes virus infection type 2 have not been calculated. An estimate based on available evidence is that they could not be considered economically balanced in relation to medical care as a whole.</p> |
| <p>15. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards</p> | <p>Realistic and detailed plans for managing and monitoring a general screening programme do not exist.</p> <p>Agreed sets of quality assurance are not available.</p> |
| <p>16. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme</p> | <p>A general screening programme would put a lot of strain on an already overstretched health care. The need for adequate staffing, facilities, treatment and programme management implies extra resources or redistribution of existent resources.</p> |

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| <p>17. All other options for managing the condition should have been considered (e.g. improving treatment, providing other services)</p> | <p>Other options for managing herpes virus type 2 infection are to put more effort into primary and secondary prevention interventions like sexual and reproductive health education and the availability of good quality health care with specialised knowledge of sexually transmitted diseases.</p> <p>In obstetric and paediatric care screening could never substitute clinical vigilance for neonatal herpes infection.</p> |
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Conclusions of the Screening report

Implications for policy

Routine serological screening for herpes virus type 2 infection in asymptomatic individuals is not ethically defensible if potential biotechnical, medical, epidemiological, psychosocial and ethical advantages and disadvantages are balanced at both the individual and public health level. Routine serological screening for herpes type 2 infection in asymptomatic individuals could thus not currently be recommended. Available serological tests are valuable diagnostic tools for individual cases as long as the medical staff is prepared to respect patient autonomy and honour the difficulties in sharing the intricate bio-epidemiology with their patients.

Implications for research

The knowledge base for herpes virus infections is patchy and very often comes from selected populations. We need to know more about the natural course of the disease and its occurrence in different population and age groups, especially in relation to herpes type 1 infection but also other sexually transmitted diseases.

People's perceptions of genital herpes need to be better known to tailor care and prevention efforts to local conditions.

Research on vaccine and vaccination programmes is important, since prevention by an effective vaccine should be the best option for public health action.

Recommendations to be considered by the NSC

It is very evident for the case of screening for asymptomatic herpes type 2 infection that screening is not just a medical activity. As all sexually transmitted diseases genital herpes carry a social stigma. Screening could result in a distortion of public belief because people might believe that a cure exists. Strategies for managing genital herpes infection at a population level need to be tailored to the local context and take into consideration the dynamics of an infectious disease. Universal serological screening would apparently be inappropriate at least in northern European countries. European countries should not be rushed into screening on the basis of evidence accrued in the United States alone.

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