

Genital herpes vaccines—cause for cautious optimism

Lewis J. Haddow^A and Adrian Mindel^{A,B}

^ASexually Transmitted Infections Research Centre, Marian Villa, Westmead Hospital and University of Sydney, Westmead, NSW 2145, Australia.

^BCorresponding author. Email: adrianm@icpmr.wsahs.nsw.gov.au

Abstract. The high prevalence of herpes simplex virus infections in many communities, its numerous serious physical and psychological complications and its importance in enhancing the transmission of HIV make this virus an obvious target for prevention by vaccination. Randomised clinical trials of only one genital herpes vaccine has shown efficacy so far. Analysis of clinical results is complicated by the difference between disease and infection, different results for males and females and the interaction between HSV-1 and HSV-2 immunity.

Introduction

The development of an effective vaccine against genital herpes is one of the most exciting advances in herpes medicine in recent years. The high prevalence of herpes simplex virus (HSV) infections in many communities, its numerous serious physical¹ and psychological complications² and its importance in enhancing the transmission of HIV³ make this virus an obvious target for prevention by vaccination.⁴ However, as is so often the case when treating herpes, each new piece of information serves to raise more questions than it answers.

Published data

The only randomised clinical trials of a vaccine against genital herpes showing efficacy so far, are those of the HSV-2 glycoprotein-D–alum–MPL vaccine (Simplirix) developed by GlaxoSmithKline (GSK).⁵ These studies, with a combined total of 2714 vaccinated subjects aged 18–45 years, demonstrated that the vaccine was over 70% effective in preventing genital herpes disease, but only in women who were seronegative for both HSV-1 and HSV-2 before receiving the vaccine. Another vaccine containing HSV-2 glycoprotein B2 and D2, combined with the adjuvant MF59, failed to show efficacy in preventing HSV acquisition; HSV disease was not reported as an endpoint in these trials.⁶

The difference between herpes disease and herpes infection, and the subtleties of the results' analysis, are crucial in interpreting the published studies. Whereas the GSK vaccine's efficacy against disease showed statistical significance in HSV-1 and HSV-2 seronegative females, the 95% confidence limits for percentage efficacy against infection just crossed zero, with *P*-values of 0.06 and 0.07 in the two studies. It is possible, therefore, that the study

was insufficiently powered to detect a difference in infection rates between the vaccine and placebo. Partly in response to this, a larger phase III study of 7550 all-female subjects is ongoing.

Vaccine immunology

Vaccines, in general, prevent disease rather than infection and they often do so in a way that reproduces naturally occurring immunity. Previous HSV-1 infection protects against HSV-2 disease, reducing its severity.⁷ An effective vaccine may in some way mimic the immunological process underlying this phenomenon. It appears that in HSV-1 seropositive, HSV-2 seronegative recipients, the GSK vaccine provided no additional protection over their normal, presumably HSV-1-induced, immunity.

The primary endpoint of the trials of GSK's vaccine was the occurrence of genital herpes disease and no distinction was made between HSV-1 and HSV-2 as causative agents. As HSV-1 is responsible for a large proportion of primary genital herpes episodes, it is entirely possible that recipients of the vaccine who are seronegative for both viruses may be protected against disease caused by either virus. The demonstration of such cross-protection would further increase the importance of the vaccine.

The sex difference in the efficacy of the GSK vaccine is intriguing. The reasons for this difference may be behavioural, but it is so striking that this seems an unlikely supposition. A physiological explanation would be supported by the finding that HSV-2 seroprevalence appears to be higher in women than among men with the same number of sexual partners.⁸ Anatomical differences between men and women are immediately obvious and the lack of a stratum corneum in the cervical mucous membrane, the protective role of vaginal flora and the larger potential surface for infection

may be implicated. An anatomical explanation would be further supported if there were a difference in HSV-2 prevalence between circumcised and uncircumcised males. However, to date, no such association has been demonstrated. Such mechanisms may explain differences between sexes in terms of acquisition and clinical presentation of genital herpes, but they are less plausible than cellular or molecular differences between the immune responses of males and females.

Induction of T helper cell type 1 (Th1) responses involving CD4 lymphocyte function appears to be important for the control of HSV infection.^{9,10} The less successful gB–gD–MF59 vaccine was shown to cause high titres of antibodies in subjects,⁶ which may relate to a more vigorous T helper cell type 2 (Th2) response and consequently a weaker Th1 response. It may be, therefore, that the female immune responses to HSV vaccination are more biased towards Th1 and CD4 cell responses. Finally, there may be interplay between cellular and anatomical mechanisms, women's responses being better adapted to prevention of HSV acquisition and disease through their specific genital anatomy.

Public health perspectives in Australia and overseas

Asymptomatic viral shedding is the most important way in which genital herpes is transmitted.¹¹ Consequently, it is not clear whether the prevention of disease, without corresponding prevention of asymptomatic infection, will reduce the overall rates of asymptomatic shedding in recipients of HSV-2 vaccine. This, in turn, has implications for prevention of onward transmission and control of the infection within the wider population. The new, larger study contains nested sub-studies, which aim to go some way towards answering these questions.

All of these clinical, physiological and public health questions raised by the published HSV vaccine trials have implications for how such a vaccine should be introduced into health care. Like many other vaccines, provision of a herpes vaccine requires the consent of individual recipients, but has much wider public health objectives and consequences.

It is thought that HSV-1 is commonly acquired in childhood in Australia and an HSV-2 vaccine with no efficacy in HSV-1 + HSV-2 recipients may be of little public health benefit unless it is provided at a young age. A recent population-based survey of Australian adults over 25 years has shown HSV-1 seroprevalence of 76%.¹² Although comparable data regarding HSV-1 seroprevalence in young people in Australia are lacking, rates have declined in Europe in recent years.¹³ This may be due to changes in hygiene, reduced family size or increased awareness of transmission of 'cold sore virus' to children. Whatever the causes, one possible consequence is that HSV-1 has increased as a cause of genital herpes^{14,15} and oral sex between adolescents may

no longer be a 'safe sex' practice. Genital herpes due to HSV-1 is a particularly frequent problem among women and the under 25 s. Providing the increasing pool of HSV-1-naive adults with enhanced protection against HSV-2 is now a greater priority than ever.

It appears fortuitous that HSV vaccine studies so far only show clinical benefit in females. Concerns about maternal transmission causing neonatal herpes may make a vaccine more attractive to women. It is conceivable that the vaccine could be implemented in similar ways to Rubella vaccination, namely by immunising all adolescent girls before the onset of sexual activity, or by serological screening in early pregnancy in order to vaccinate susceptible women. A recent study has shown that concerns about safety are a major barrier to uptake of a herpes vaccine by women, and the risks and benefits will need to be carefully presented in order to overcome this barrier.¹⁶ An additional concern is that the stigma of lifelong herpes infection is so great that a vaccine that prevents disease but not infection may be less attractive to young adults.

Public perceptions of, and political barriers to, immunisation against genital herpes need to be considered. Parents are usually the main decision makers in their children's health care and providing a vaccine to adolescent girls with the specific aim of preventing genital herpes is liable to raise considerable anxieties. Our own experience of working on a detailed safety study of HSV-2 glycoprotein-D–alum–MPL vaccine in adolescent girls has made us acutely aware of the complex and often impenetrable issues in this area. Despite the current policy of routinely immunising adolescents against hepatitis B, also an STI, the prospect of a vaccine protecting against herpes may provoke fears that it will 'encourage' unsafe sex, as well as being a taboo subject for discussion between parents and children. Safety fears relating to new variant Creutzfeldt-Jakob disease, responses to the recent measles–mumps–rubella vaccine crisis in the UK and the longstanding anti-vaccination and homeopathic lobbies, may also limit progress in herpes vaccine provision. Research in the USA found white, university-educated, professionally-employed parents to be less likely to accept a vaccine against an STI for their children.¹⁷ It will be vital for public health policy-makers to consider whether a suboptimal mass vaccination program or a strategy focussed on specific groups is likely to be more beneficial.

Outside Australia, there are considerable variations in the prevalence of HSV-1 and HSV-2. Studies in Europe and the USA have reported increasing rates of HSV-1 as a cause of genital herpes,¹⁸ with ethnic variations within the USA and the UK between the relative prevalence of the two types.¹⁹ Across Europe there are different patterns of HSV-1 and HSV-2 seroprevalence according to age and sex; as high as 83.9% HSV-1 and 23.9% HSV-2 seroprevalence in Bulgaria in small selected studies.²⁰

Studies demonstrating the high rates of genital herpes disease and infection due to HSV-2 in African countries highlight the potential need for an effective vaccine against the disease.²¹ Costs are a fundamental problem, however, and a herpes vaccine program may be lower priority when compared with the many other health needs of developing countries. It has been observed that immune cells in the base of herpetic ulcers are highly suited to both infection with, and shedding of, HIV virions.^{22,23} This feature is so marked that it has been estimated that 19–74% of all HIV infections are transmitted by herpes ulcers in some African countries.^{24–26} The possibility that a vaccine against genital herpes might prevent HIV transmission on an individual or population level is the subject of ongoing research and could vastly increase the benefits of a vaccine and make the costs much more worthwhile. Unfortunately, there is such a high HSV-1 prevalence in these areas that a vaccine, which is ineffective in people with prior infection, would likely be of no benefit.

Future directions

We have raised several questions that could be answered by further research, some of which are currently under study. It appears from published trials that the adjuvant contained in the preparation is central in inducing a clinically beneficial immunological response. The type, degree and duration of immune response are crucial for any vaccine and there are marked differences between adjuvants in these regards. Further understanding of the mechanisms of the HSV immune responses in men and women and in animals will inform future vaccine development. This may also help develop better-validated surrogate markers of immunogenicity. The interaction between HSV-1 and HSV-2 immunity may also be important in understanding how to provide protective immunity against HSV-2 in HSV-1 + HSV-2 negative individuals.

Alongside basic science and clinical research, work will need to be done to determine how best to implement the vaccine development in Australia and other countries. Cost-benefit analysis may need to examine different vaccination strategies, whether these are targeted at particular age or ethnic groups, and how frequently individuals should be immunised. Whether a mass-vaccination strategy or a targeted approach is to be adopted, policy-makers must consider how best to 'sell' the vaccine. Targeted strategies might aim at women planning a pregnancy, adolescents, partners of HSV carriers, be user-demand led, or be preceded by blood testing to check HSV-1 serostatus, although such a measure may raise considerable anxieties, costs and problems with processing and interpretation of tests.

We now have an effective vaccine against genital herpes, a most distressing chronic viral illness. It seems that this vaccine will be able to protect some vulnerable

individuals, but it falls short of being an ideal product to protect the public from the rising rates of genital herpes. The suggestion of its use as a method of preventing HIV transmission is exciting but somewhat speculative at present. There are several unanswered questions relating to the immunological properties of current vaccines, which need to be resolved before more useful products can be developed. Even then, the difficult task of finding a place for the HSV vaccine in the public health arena remains to be tackled.

Conflict of interest

The authors are investigators on a GlaxoSmithKline study of the safety and immunogenicity of a vaccine to prevent genital herpes in adolescent girls (HSV-040).

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