

## Herpes simplex virus vaccines



Prof. Adrian Mindel  
Director, Sexually Transmitted Infections  
Research Centre, Westmead Hospital

Email: [adrianm@icpmr.wsahs.nsw.gov.au](mailto:adrianm@icpmr.wsahs.nsw.gov.au)  
Tel: (02) 9845 6286

Herpes simplex virus (HSV) infections are among the commonest human infections. HSV type 1 (HSV-1), the common cause of cold sores, is usually transmitted primarily in childhood though salivary contact; whereas HSV-type 2 (HSV-2) the common cause of genital herpes, is sexually transmitted in adolescents and adults. For many individuals HSV infections are a minor nuisance, but genital herpes can be a cause of considerable psychosexual dysfunction. In addition, HSV infections are leading causes of blindness worldwide and neonatal infections and herpes encephalitis are associated with high mortality and often, ongoing morbidity in survivors. Finally, HSV-2 is now considered to be a major cofactor in the transmission of HIV.

Numerous so-called vaccines have been suggested to prevent herpes infections, ranging from inactivated virion derived vaccines, adjuvanted subunit vaccines, vectored vaccines, replication limited live viral vaccines, genetically attenuated live viral vaccines, and nucleic acid vaccines. Most have not been tested in clinical trials.

There have been several randomised placebo controlled trials (RCT) using subunit vaccines against genital herpes. However, the only RCTs showing efficacy so far, are those of the HSV-2 glycoprotein-D–alum–MPL vaccine (Simplirix) developed by Glaxo Smith Kline (GSK). These two studies, with a combined total of over two and a half thousand subjects aged 18-45, 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 2 prior to receiving the vaccine. The primary endpoint was the occurrence of genital herpes disease and no distinction was made between HSV-1 and HSV-2 as causative agents. HSV-1 is now responsible for a large proportion of primary genital herpes episodes and it is entirely possible that vaccine recipients, 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. Partly in response to these results, a larger phase III study, involving almost eight thousand young women, is ongoing.

Another vaccine containing HSV-2 glycoprotein B2 and D2, combined with the adjuvant MF59, in two RCTs, did not show efficacy in preventing HSV acquisition. However, HSV disease was not reported as an endpoint in these trials.

Most vaccines prevent disease rather than infection, probably by reproducing naturally-occurring immunity. Previous HSV-1 infection appears to offer some protection against HSV-2 disease and 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

One of the most intriguing aspects of the GSK vaccine's efficacy is the difference between men and women. The reasons for this difference may be behavioural, but it is so striking that this seems unlikely. The finding that in most communities, HSV-2 seroprevalence is higher in women than in men with the same number of sexual partners would support a physiological and/or anatomical explanation. In women, lack of a stratum corneum in the cervical mucous membrane, the protective role of vaginal flora and the larger potential mucous membrane surface for infection may be important. Another possible explanation relates to the 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. The unsuccessful gB–gD–MF59 vaccine was shown to cause high titres of antibodies in subjects, which may relate to a more vigorous T helper cell type 2 (Th2) response and consequently a weaker Th1 response. Therefore it may be that the female immune responses to HSV vaccination are more biased towards Th1 and CD4 cell responses. The most likely explanation is that there is interplay between immunological, physiological and anatomical mechanisms, with women's responses being better adapted to prevention of HSV acquisition and disease than men's.

Asymptomatic viral shedding is the most important way in which genital herpes is transmitted and occurs in individuals who have clinically overt recurrences as well as those who have no signs or symptoms of infection. Consequently, it is not clear whether, in recipients of HSV-2 vaccine, the prevention of disease, without corresponding prevention of asymptomatic infection and its associated viral shedding, will be important in reducing the risk of onward transmission within the wider population.

The 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.

HSV-1 is commonly acquired in childhood and an HSV-2 vaccine with no efficacy in HSV 1+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 has shown HSV-1 seroprevalence of 76 %. Although comparable data regarding HSV-1 seroprevalence in young people in Australia are lacking, rates have declined in Europe in recent years. This may be due to improvements in hygiene, reduced family size or increased awareness of transmission of "cold sore virus" to children. One possible consequence is that HSV-1 has increased as a cause of genital herpes via oro-genital sex. Genital herpes due to HSV-1 is now a particularly frequent problem amongst women and the under-25s. Providing the increasing pool of HSV-1-naïve 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 young girls prior to the onset of sexual activity.

Cont.



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 may raise considerable anxieties. Despite the current policy of routinely immunising adolescents against hepatitis B, also a 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. Recent safety fears relating to links between autism and the measles-mumps-rubella vaccine in the UK and the longstanding anti-vaccination and homeopathic lobbies may also limit progress in herpes vaccine provision.

Studies demonstrating the high rates of genital herpes disease and infection due to HSV-2 in many African countries and the role of HSV 2 in HIV transmission highlight the potential need for an effective vaccine against HSV 2. It has been observed that immune cells in the base of herpetic ulcers are highly susceptible to infection with, and shedding of, HIV virions. This feature is so marked that some African countries, it has been estimated that 19-74% of all HIV infections are transmitted in association with herpetic ulcers. The possibility that a vaccine against genital herpes might prevent HIV transmission at 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 be unlikely to be of benefit. Costs are also a fundamental problem and a herpes vaccine programme may be lower priority when compared to the many other health needs of developing countries

Where do future priorities lie? 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, perhaps 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 pre-adolescents, adolescents, partners of individuals with HSV infections, women planning a pregnancy, 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, that could protect over 70% of susceptible 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 remains speculative. There are a number of unanswered questions relating to the immunological properties of current vaccines, which need to be answered 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.

### Grant Successes

We are proud to announce that members of CIDM Public Health staff are Chief Investigators for the following successful grants:

#### ARC Linkage Grants 2006-2008

- Economic and social benefits of treating and preventing influenza in aged care facilities.
- Informatics approaches to improving risk assessment and response to outbreaks of communicable diseases.

#### NHMRC Urgent Projects 2006

- Novel, high throughput platform for rapid identification, quantitation, differential diagnosis, and resistance testing of influenza
- Development of National Protocols for the Detection of Influenza A H5N1
- Use of rolling circle amplification, ligase chain reaction and real-time PCR to detect neuraminidase inhibitor resistance.
- A prospective study to examine the effectiveness and safety of antivirals against pandemic influenza
- Assessment of interventions for controlling pandemic influenza and determining data needs to inform these assessments

### STAFF PROFILE HEATHER GIDDING



Heather Gidding  
Epidemiologist, CIDM Public Health

Tel: (02) 9845 6255

Email:  
heatherg@icpmr.wsahs.nsw.gov.au

Heather started working as an epidemiologist with CIDM Public Health in 2004. Prior to this she studied for her Masters of Applied Epidemiology at the Australian National University and worked for five and a half years as an Epidemiology Fellow at the National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases (NCIRS) where she was involved in the monitoring and reporting of national surveillance data to describe the epidemiology of vaccine preventable diseases.

This required working with large data bases, the SAS, Access and SPSS. She was also involved in the coordination of the national serosurveillance program and used the results of the varicella serosurvey to model the impact of proposed vaccination strategies.

At CIDMPH Heather has contributed to development of databases to facilitate data retrieval and analysis, she has been involved in the planning new projects, assisting with the preparation of grant applications and undertaking analysis of results of existing projects. She has also continued to work on serosurveillance projects conducted as part of our collaboration with the NCIRS. These activities have enhanced our research capacity by improving study and database design and increasing our ability to answer relevant epidemiological research questions. Heather conducts lectures at the University of Sydney for the Masters of Public Health & International Public Health (Vaccines and Public Health elective); she has also has conducted tutorials in statistics and the use of EpiInfo and Microsoft Access for CIDM-PH research staff.

### CIDM PUBLIC HEALTH SYMPOSIUM SERIES & EDUCATION PROGRAM

**31 March: Sexually Transmissible Infections Symposium**  
(Keynote Speaker: Prof. Ian Frazer – Australian of the Year)  
**10 May: Influenza Workshop**  
**18 Aug: Vaccine Preventable Diseases Symposium**  
**03 Nov: Multi Resistant Organisms Symposium**

To join our e-list to receive updates please email  
judithh@icpmr.wsahs.nsw.gov.au