**CSIRO** PUBLISHING & **MINNIS** COMMUNICATIONS
www.publish.csiro.au/journals/sh

*Editorial*

*Sexual Health*, 2006, **3**, 63–65

# Human papillomavirus vaccines: challenges to implementation

*Suzanne M. Garland*

Department of Microbiology and Infectious Diseases, Department of Microbiological Research, Royal Women's Hospital, 132 Grattan St, Carlton, VIC 3053, Australia. Department of Obstetrics and Gynaecology, University of Melbourne, VIC, Australia. Email: suzanne.garland@rch.org.au

**Abstract.** Clinical trials for prophylactic human papillomavirus (HPV) vaccines have shown overwhelmingly positive results. It is expected that with good coverage of the vaccine, 70% of cervical cancers will be prevented, as will a proportion of other HPV-related anogenital diseases. Issues that will require careful consideration will include: whether males and females should be vaccinated; the durability of the immune response; the proportion of attributable disease to the HPV types targetted by the vaccines; and accessibility and cost of the vaccine. Central to an effective vaccination programme will be clear, concise and consistent educative messages regarding HPV not only to the lay public, but also the medical profession.

It is very likely that prophylactic human papillomavirus (HPV) vaccines will be made available this year, because phase-2 and -3 clinical trial data of such HPV vaccines show overwhelmingly positive results, in those initially seronegative and HPV DNA negative for vaccine types.[1–4] In the original proof of principle trial, monovalent, non-infectious, recombinant viral-like particle (VLPs) HPV-16 vaccine was safe, well tolerated and highly effective, giving 100% protection for persistent HPV-16 infection and related cervical intraepithelial neoplasias (CIN).[1] Subsequently, a phase-2 trial of a bivalent VLP HPV-16/18 vaccine has shown similar protection for persistent infection and related disease from these two viral types.[3] However, the earlier proof of principle studies were not powered to demonstrate vaccine efficacy with respect to clinically relevant HPV-related disease (CIN). Excitingly, interim results of several phase-3 clinical vaccine efficacy trials of a quadrivalent vaccine including VLPs with HPV types 6, 11, 16 and 18 has been presented at recent conference proceedings and demonstrated not only to give complete protection against HPV-16/18-related CIN 2/3, adenocarcinoma *in situ*, and cancer through 2 years of post-vaccination follow-up,[5] but also protection against other HPV-related genital dysplasias and neoplasias (vulval intraepithelial neoplasias (VIN) and vaginal intraepithelial neoplasias (VAIN)) as well as against genital warts (predominantly caused by HPV genotypes six and 11).[6]

All such studies of prophylactic HPV L1 VLP vaccines in healthy adult women have demonstrated almost universal seroconversion in vaccinated subjects[1–6] with neutralising antibody responses substantially higher than that resulting from natural infection and with vaccine protection against persistent HPV-16 infection and HPV-16-related CIN 2/3 for at for at least 3.5 years after immunisation.[2]

These vaccines have primarily been trialled in young, healthy females aged 16 to 24 years. As they are prophylactic vaccines, it would be preferable to use them prior to HPV exposure, which occurs commonly after sexual debut. Therefore, the most appropriate age group for vaccination will be between 9 and 12 years, prior to becoming sexually active.[7] Central to all the challenges facing HPV vaccination is education of the community and health care providers. That is, education regarding the relationship between genital oncogenic (or high risk) HPV infections, cervical dysplasia and cancer will need to be carefully addressed. Some members of the public may be uneasy vaccinating young girls, particularly as it becomes more generally known that HPV is sexually transmitted. In this issue of the journal, the article by McClelland and Liamputtong describes using a qualitative approach, exploring the knowledge and attitudes of sexually transmitted infections, HPV vaccination and vaccine acceptability, and factors influencing acceptance among seven men and seven women aged between 18 and 23 years in Melbourne.[8] Their findings suggest that although knowledge of HPV is inadequate, it was not found to have any impact on purported vaccine acceptance, which was reported as high. Furthermore, there were no clear gender differences found in HPV or vaccine knowledge or vaccine acceptance. Although vaccination was generally viewed positively by the young men and women involved in this study, the health beliefs of these individuals had been shaped largely by a number of factors, including cost of the



10.1071/SH06018 1448-5028/06/020063

vaccine, its access and the individual's perceived personal susceptibility to the virus.[8] In a further, recently conducted study of ninety women aged 18–30 years from metropolitan Melbourne, these authors showed that although many women do not understand the risk factors for HPV infection, the clinical problems it may cause and the potential long-term complications of infection, including cervical cancer, respondents demonstrated a good understanding of the Pap test and interpretation of an abnormal result.[9] Encouragingly though was that although very few women had heard of a potential HPV vaccine, most surveyed stated they would approach their general practitioner for more information, if one became available. This reported high level of trust in health care practitioners as sources of information and advice about HPV suggests the importance that health care providers will make in developing health promotion and education programs.

Globally, the greatest impact of the prophylactic vaccines will be in low-resource settings where cervical cancer is the leading cause of cancer death among women. Yet, cervical cancer is highly preventable through cytology screening programs, although in resource-poor countries, cytology screening is either nonexistent, has inadequate population coverage or inadequate quality control to have an impact on cervical cancer incidence and mortality. Fortunately, in Australia, with good coverage and high quality assurance cervical cytology Pap programmes have resulted in marked reductions, with cervical cancer falling to the 18th most common cause of cancer death in women.[10] The incidence of cervical cancer remains higher, however, among indigenous Australians than for other Australian women, likely a result of poorer access to services. In Australia, almost 900 (868) new cases of cervical cancer occur annually with 262 deaths (mortality rate of 2.8 per 100 000 women in 2001). In 2000–2001, 3 314 787 women participated in cervical screening in Australia, with 61.8% of Australian women in the target age group of 20–69 years. High-grade abnormalities were detected in 13 555 women, at a rate of 10 per 1000 women screened detected in women aged less than 35 years of age: such lesions are caused by high-risk HPVs.[11]

It is expected that with good coverage of the vaccine, 70% of cervical cancers will be prevented by vaccination, a similar proportion to an effective Pap screening program. Moreover, a proportion of CIN, as well as VIN, and, if the quadrivalent Gardasil™ vaccine is used, a high proportion of genital warts, will be prevented. Although we await the results of ongoing studies in men, there is the potential to reduce the anal intraepithelial neoplasia (AIN) as well as anal cancer, diseases of particular relevance in men who have sex with men. Therefore, for countries like Australia with good screening programmes, pertinent questions that arise before rolling out such a vaccine include: under what conditions is HPV vaccination likely to be cost-effective? And how should current screening programs be modified? Various cost effective analyses and models have been developed overseas in the context of current cervical cancer screening programs. For example, Goldie *et al*.[12] from the USA evaluated vaccination at age 12 (under various assumptions of efficacy, waning immunity, and competing infection with non-16/18 types) in combination with different Pap smear screening strategies that varied by start age and frequency. Although the results were sensitive to various assumptions of duration of immunity, the authors concluded that a program of HPV-16/18 vaccination at the age of 12, coupled with triennial Pap screening starting at age 25, would decrease lifetime risk of cervical cancer by 94% and was the most cost-effective strategy.[12] Furthermore, Kulasingam and Myers[13] developed a Markov model to evaluate the impact of HPV vaccination on screening programs in the USA. Strategies of vaccination alone at age 12, cytology screening alone, and vaccination followed by screening were evaluated under various assumptions about duration of vaccine immunity, screening start age, and frequency. Similar to the analysis by Goldie *et al*.,[12] the authors found that a strategy of vaccination followed by delayed onset of Pap screening at age 24 was the most cost-effective strategy under base case assumptions of 75% effectiveness and 10-year immunity.[13] Ultimately, a combination of vaccination and cervical cytology, albeight it with modified age of commencement and increased intervals, will be most effective in the prevention of HPV related genital diseases.

Other important challenges and issues requiring careful consideration prior to the widespread introduction of a prophylactic HPV vaccine include: whether males and females should be vaccinated; the durability of the immune response; the proportion of attributable disease to the HPV types targeted by the available vaccines; and the accessibility and cost of the vaccine, particularly for the developing world where the greatest burden of disease from cervical cancer exists. Furthermore, given that there are two major pharmaceutical manufacturers producing prophylactic HPV vaccines (Merck (Gardasil™) and GlaxoSmithKline (Cervarix™)), the former with a focus on targeting cervical cancers and genital warts, and the latter purely targetting cervical cancers, even assuming the vaccines to be of similar price, there will be a dilemma in which vaccine to choose.

Although the data from phase-3 clinical trials to date have only reported on those naive to vaccine-related HPV DNA and HPV antibodies, vaccines were trialled in women who are sexually active with up to five partners.[1–4] A proportion of the vaccinated population will have had either pre-existing HPV DNA positivity and/or HPV seroprevalence positivity for the vaccine types. We wait with interest the outcome of these data to give insight into whether sexually active women

could benefit from vaccination. Moreover, there are ongoing mature-age women vaccination trials in progress that will answer these questions. In the article also in this issue of *Sexual Health*, O'Keefe *et al*. reported on the prevalence of genital HPV DNA in a sample of senior school-aged sexually active women, 16 to 19 years of age in the Australian Capital Territory.[14] They reported a prevalence overall of 11.2% with high-risk genotypes in over half, and multiple genotypes in 38%. This rate is lower than that reported in some comparable populations in other countries. These findings also suggest that vaccination of young sexually active women may well have a place. Although Australia has achieved very high levels of vaccination coverage for childhood infections in the past 10 years, with 91% of children fully vaccinated at 12 months of age, in the first instance HPV vaccine will be targetted to young girls around nine to 12 years of age.[15] Although worldwide delivery of childhood vaccines to infants has been reasonably well rolled out, the immunity from HPV vaccine will need to prove long-standing durability before it could be included in this age group. Therefore, implementation will require efficient delivery systems such as school-based programs. The development of viral-like particle technology, which has led to the HPV vaccine by the Australian of the Year, Professor Ian Frazer, and the recent demonstration of the safety and effectiveness of new HPV vaccines, is a major breakthrough in medical science. Implementation of this prophylactic vaccine is a public health tool that has the potential to prevent a large proportion of cases of the number two cancer killer of women in the world, cervical cancer, and has the potential to reduce the morbidity and clinical cost of other HPV-related anogenital diseases.

## Note added in proof

[22 May 2006]: The USA's FDA gave initial approval for Gardasil on 19 May 2006.

## Conflicts of interest

Suzanne Garland is a member of the advisory boards for both CSL (CSL GARDASIL Advisory Board) and GlaxoSmithKline (Cervical Cancer Prevention Working Group).

## References


1 Koutsky LA, Ault KA, Wheeler CM, Brown DR, Barr E, Alvarez FB, *et al.* Proof of Principle Study Investigators. A controlled trial of a human papillomavirus type 16 vaccine. *N Engl J Med* 2002; 347(21): 1645–51. doi: 10.1056/NEJMoa020586

2 Mao C, Koutsky L, Ault K, Wheeler C, Brown D, Wiley D, *et al*., for the Proof of Principle Study Investigators. Efficacy of human papillomavirus-16 vaccine to prevent cervical intraepithelial neoplasia. A randomised controlled trial. *Obstet Gynecol* 2006; 107(1): 18–27.

3 Harper DM, Franco EL, Wheeler C, Ferris DG, Jenkins D, Schuind A, *et al*., and the GlaxoSmithKline HPV Vaccine Study Group. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet* 2004; 364(9447): 1757–65. doi: 10.1016/S0140-6736(04)17398-4

4 Villa LL, Costa RL, Petta CA, Andrade RP, Ault KA, Giuliano AR, *et al*. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16 and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. *Lancet Oncol* 2005; 6(5): 271–8. doi: 10.1016/S1470-2045(05)70101-7

5 Skjeldestad F for the FUTURE II Steering Committee; Dept of Epidemiology, SINTEF Health Research, Trondheim, Norway. Prophylactic Quadrivalent Human Papillomavirus (HPV) (Types 6, 11, 16, 18) L1 Virus-Like Particle (VLP) Vaccine (Gardasil™) Reduces Cervical Intraepithelial Neoplasia (CIN) 2/3 Risk. Abstract 43rd Annual Meeting of Infectious Diseases Society of America, October 6–9, 2005, San Francisco, CA. [Abstract]

6 Harper D. for the FUTURE I investigators. Efficacy of a Prophylactic Quadrivalent Human Papillomavirus (HPV) (Types 6, 11, 16, 18) L1 Virus-Like Particle (VLP) Vaccine for Prevention of Cervical Dysplasia and External Genital Lesions (EGL) 45th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy, December 16–19, 2005, Washington, DC.

7 Smith AMA, Rissel CE, Richters J, Grulich AE, de Visser RO. Sex in Australia: first experiences of vaginal intercourse and oral sex among a representative sample of adults. *Aust N Z J Public Health* 2003; 27(2): 131.

8 McClelland A, Liamputtong P. Knowledge and acceptance of human papillomavirus vaccination: perspectives of young Australians living in Melbourne, Australia. *Sex Health* 2006; 3(2): 95–102. doi: 10.1071/SH05035

9 Giles M, Garland SM. A study of women's knowledge regarding human papillomavirus virus (HPV) infection, cervical cancer and HPV vaccines. ANJOG 2006.

10 Australian Institute of Health and Welfare (AIHW) Cervical Screening in Australia 2002–2003. AIHW Cat. No. 26. Canberra: Australian Institute of Health and Welfare; 2005. (Cancer Series Number 31).

11 Australian Institute of Health and Welfare (AIHW). Cervical screening in Australia 2000–2001 and 1999–2000. AIHW Cat. No. 19. Canberra: Australian Institute of Health and Welfare; 2003. (Cancer Series Number 24).

12 Goldie SJ, Kohli M, Grima D, Weinstein MC, Wright TC, Bosch FX, Franco E. Projected clinical benefits and cost-effectiveness of a human papillomavirus 16/18 vaccine. *J Natl Cancer Inst* 2004; 96(8): 604–15.

13 Kulasingam SL, Myers ER. Potential health and economic impact of adding a human papillomavirus vaccine to screening programs. *JAMA* 2003; 290(6): 781–9. doi: 10.1001/jama.290.6.781

14 O'Keefe E, Currie MJ, Garland SM, Tabrizi S, Bowden FJ. Prevalence of genital human papillomavirus DNA in a sample of senior school-aged women in Australian Capital Territory. *Sex Health* 2006; 3(2): 91–4. doi: 10.1071/SH05047

15 Medicare Australia. Australian Childhood Immunisation Register Statistics. Coverage. Available online at: www.medicareaustralia.gov.au/providers/health_statistics/statistical_reporting/acir.htm [verified May 2006].


Received 14 March 2006, accepted 21 March 2006