

Planning for human papillomavirus vaccines in Australia

Report of a research group meeting

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Background

Human papillomavirus (HPV) is the most common viral sexually transmitted infection, with estimates that up to 75 per cent of people are infected at some time.¹ Whilst most infection resolves without symptoms, some human papillomavirus infections can persist and cause cancer. In particular, the role of HPV infection in causing cervical cancer, the second most common cause of cancer in women worldwide, is undisputed. HPV exists as over 200 types but only some of these types are oncogenic (causing cervical, other anogenital cancers, oral and laryngeal cancers.) Other common HPV types cause skin warts.

The recent development of vaccines to protect against infection with oncogenic HPV types holds promise for the primary prevention of both cervical cancer and its precursors. The vaccines are based upon the Australian discovery that the major HPV capsid protein L1 can self assemble into virus-like particles (VLPs) when independently expressed in cultured cells,² and induce high titres of type-specific and protective neutralising antibodies in animals. These VLPs lack any viral genetic information and are not infectious. VLP based vaccines against the cancer causing HPV types 16 and 18, and against types 6 and 11 (which cause genital warts) are in current clinical trials. Early results are promising, with vaccine providing 100 per cent protection (95% CI 90-100%) against persistent infection with HPV 16.³ These vaccines are likely to become available in the next few years. According to a recent meta-analysis of worldwide prevalence data, vaccinating against HPV 16 and HPV 18 could prevent over 70 per cent of invasive cervical cancers worldwide.⁴

Human papillomavirus research meeting objectives

With a view to initiating discussion and research into the possible future role of HPV vaccines in Australia, on 12 December 2003, the National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases brought together representatives from eight Australian research groups currently involved in HPV research and both vaccine manufacturers with current HPV vaccine candidates. The two main objectives of the meeting were:

1. to identify information needs and research priorities to inform national vaccination policy decisions; and
2. to foster links between research groups.

Current state of vaccine development

During the meeting, updates on vaccine development and trial results were discussed, with results to date indicating that the vaccines are effective in preventing persistent infection with targeted HPV types, induce high titres of protective antibody (Geometric Mean Titre 80-100 times those seen in natural infection) and are safe.

Epidemiology and burden of illness

Approximately 470,000 cases of cervical cancer and 235,000 deaths occurred worldwide in 2000.⁵ Most of this disease occurs in the developing world. In Australia, cervical cancer is the eleventh most

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common cancer in women. Almost 800 new cases occur annually (incidence rate 2000, 7.1 per 100,000 women) with 262 deaths in 2001.⁶ A disproportionate burden of cervical cancer is borne by Indigenous women and some ethnic groups within Australia. The age-standardised death rate from cervical cancer in Aboriginal women in Western Australia, South Australia, Queensland and the Northern Territory from 1998–2001 was over four times the rate for non-Indigenous women (11.4 per 100,000 compared to 2.5 per 100,000 non-Indigenous women).⁶

During 1999/2000 63 per cent of Australian women aged 20–69 years participated in the National Cervical Screening Program, resulting in the detection of approximately 200,000 low grade lesions, 14,000 high grade lesions, and 99 cases of micro-invasive cervical cancer. During this period 646 cases of invasive cancer and 249 cervical cancer deaths were documented.⁶

International prevalence surveys of HPV types in invasive cervical cancer have shown that the most common types of HPV found in cancers are types 16 and 18.^{4,7} Geographical variation in prevalence of various HPV genotypes in cancers, as well as in HPV carriage of cytologically normal populations, has been noted. For example, HPV 18 is more common in cancers in Indonesia, whilst types 52 and 58 are more common in Asia. Three studies of genotypes in invasive cervical cancer in Australia determined using polymerase chain reaction (PCR) have been published. Chen, *et al* (1999) in Melbourne, screened tumour tissue of 186 women with invasive cervical cancer, for HPVs and found that 91.9 per cent were positive using PCR.⁸ Of these, 54 per cent were HPV 16, 17 per cent HPV 18 and 21 per cent other types. In 1994, Thompson, *et al*, detected HPV using a different PCR in 89 of 103 cancers (86%) with HPV 16 in 65 per cent, HPV 18 in 18 per cent and HPV 31 in three per cent in women residing in Sydney.⁹ More recently, Liu, *et al* (2003) detected HPV in 90 per cent of the tumours from 79 Sydney patients with invasive cancer, with HPV 16 comprising 55 per cent, HPV 18 thirteen per cent, and coinfection with HPV 16 and 18 in 11 per cent.¹⁰ Thus HPV types causing cancer in Australia appear to reflect global consensus, although studies in Indigenous populations are yet to be undertaken.

Modelling

The continuing development of models for the natural history of HPV infection and transmission in populations, and the cost effectiveness and impact of HPV vaccination, were highlighted.^{11,12,13} These models have been developed overseas but could form the basis of local models providing that Australian data

were available. Local data requirements include HPV type specific prevalence estimates by age and sex and cervical intraepithelial neoplasia (CIN) status, local population structure and sexual mixing pattern data, screening program data (coverage, costs, efficacy), burden of disease data and costings and updated vaccine efficacy data.

Australian human papillomavirus research update

Participants at the meeting presented a diverse range of past, current and future research work in relation to HPV.

Professor Suzanne Garland (Department of Microbiology and Infectious Diseases, Women's and Children's Hospital Melbourne) outlined past projects conducted including HPV typing in high grade dysplasias and cervical cancers, research into sexual transmission by studying virgins, investigating self collected sampling methods, prevalence in Indigenous women, and in transplantation recipients.^{14–17} Current research areas include: the detection of HPV DNA post elective treatment for dysplasia and as a marker of residual or recurrent disease (as compared to current standard of care); the use of p16 and the APOT (amplification of papillomavirus oncogene transcripts) assay to detect whether HPV DNA is integrated or episomal; and evaluation of various HPV typing methods such as the line-probe assay and the HPV DNA chip and micro-array. The research group is also taking part in a multi centre randomised double-blind placebo controlled trial of a quadrivalent prophylactic HPV vaccine.

Professor Ian Frazer (Centre for Immunology and Cancer Research, University of Queensland) updated participants on current knowledge regarding the natural history of HPV infection. He highlighted findings from large cohort studies describing the incidence of infection, the chance of cervical abnormalities given infection and the risk of progression and regression.^{18,19} Over 99 per cent of oncogenic HPV infection will regress eventually. Older women with high risk HPV types have a greater chance of progression than younger women.¹⁹

Professor Frazer outlined his interest in preventing cervical cancer through preventing incident HPV infection (through vaccination) and his recent research into immunotherapy to produce resolution of CIN2/3 lesions. The Centre for Immunology and Cancer Research (CICR), in conjunction with the CSL Pharmaceuticals, has recently completed Phase 1 studies in this area of CerVax™ vaccine which is comprised of a recombinant bacterial

fusion of HPV 16 E6 and E7 proteins in 8M Urea with ISCOMATRIX® adjuvant. CICR has plans for ongoing vaccine immunotherapy trials and has recently been involved in trialling vaccination with HPV 6b L1 VLPs as a treatment for genital warts in China. CICR has taken part in a recent World Health Organization sponsored HPV serology standardisation exercise. It is also involved in ongoing collaborative basic research into HPV (animal models of cervical immunotherapy, studies on HPV uptake and presentation by dendritic cells, studies on mechanisms of innate resistance to HPV infection, siRNA therapy preclinical studies and polynucleotide vaccine preclinical studies.)

Mr Brian Brestovac (Division of Microbiology and Infectious Diseases, PathCentre) presented results from a HPV genotyping study of ThinPrep samples referred for cytology to PathCentre. Results were presented by cytology results, including 32 squamous cervical cancers and by region (Western Australia, Perth, Kimberley). Twenty-four different genotypes were identified with HPV 53 and 16 being the most common in Western Australia and differences in distribution between regions (e.g. HPV 52 only found in the Kimberley). HPV 16 was the most common genotype found in women with CIN or cancer. Mr Brestovac concluded that the distribution of HPV genotypes varies between geographical areas and that, whilst cancers are predominantly caused by HPV 16 and 18 in Western Australia, a large proportion of dysplastic lesions contain other HPV genotypes.

Professor Yvonne Cossart (Department of Infectious Diseases and Immunology, University of Sydney) highlighted HPV research undertaken with her principal collaborators, Barbara Rose and Carol Thompson. The department has produced 52 HPV related publications to date, encompassing three major research domains of natural history/epidemiology, virus genotypes and variants, and cell biology and host response. The group has produced four studies describing the genotypes that cause cervical cancer in Australia (dot-blot study of Zhang 1988,²⁰ historic cohort of cancers dating from 1922 onwards by Thompson, *et al* 1992,²¹ 1994 study by Thompson⁹ and modern cohort using PCR by Liu, *et al* 2003¹⁰). The cervical HPV prevalence and type distribution in Sydney women attending sexually transmitted diseases clinics and Family Planning Australia clinics has also been published. Two early studies using dot-blot methods typed HPV in genital warts but there have been no recent studies.^{22,23} Recently, the department has been involved in HPV typing of laryngeal papillomas and of head and neck cancer (in collaboration with the International

Agency for Research on Cancer). Other recent work has focused on cell biology and host response^{24,25} and on intratypic variation in HPV 16. Other areas of research have involved skin carriage of HPV and viral loads in immunosuppressed and non-immunosuppressed individuals. Ongoing epidemiological work includes a study of women attending clinics in outer western Sydney for Pap smears and cervical dysplasia/cancer and risk factor (including HPV) analyses for South China and Australia.

Associate Professor Freddy Sitas (Director of the Research and Registers Division at the Cancer Council NSW) described the ongoing development of a study design, in collaboration with Associate Professor Dianne O'Connell (Cancer Epidemiology Research Unit, Cancer Council NSW), Dr Carol Thompson (Department of Infectious Diseases and Immunology, University of Sydney), Professor Valerie Beral of the Epidemiology Unit, Cancer Research UK, and others. The study aims to measure the association between CIN II/III and: smoking; current prolonged use of exogenous hormones (oral contraceptives, hormone replacement therapy); seroprevalence of the leading human papillomavirus subtypes (16 and 18); and long term 'persistence' of HPV (2 tests over 14 years). The study will be a nested case-control design of approximately 7,000 women from the New South Wales Pap Test Register cohort.

Dr Elizabeth Davey (Screening Test Evaluation Program, School of Public Health, University of Sydney) gave an overview of the research components of the Screening Test Evaluation Program (STEP) (diagnostic and screening accuracy, assessment of screening outcomes and informed decision-making.) The group has been involved in HPV research in relation to HPV testing as an adjunct to Pap screening. STEP is currently undertaking a trial of 400 women attending family planning clinics in New South Wales, Queensland and the Australian Capital Territory. The study is a three arm randomised trial with participants allocated to one of three management options, either (a) HPV DNA testing; (b) repeat Pap testing; or (c) a decision aid and choice of either management (a or b). The study aims to evaluate psychosocial and quality of life/utility outcomes of triage testing by HPV DNA testing among women with mild atypia on Pap smear. The study will evaluate the women's preferences for each management (HPV testing or repeat Pap) within the decision aid arm and psychosocial outcomes in those who make an 'informed choice'.

The chief investigator, Dr Kirsten McCaffery, also has research interest in the psychosocial issues around HPV vaccination. Such issues include the acceptability of the vaccine, parental consent, health education, reducing the stigma of HPV infection and the impact of vaccination on subsequent screening behaviour, safe sex and other risk behaviours. There are several potential impacts of HPV vaccination on cervical screening that will need to be considered. These include the effect on test performance (Pap, HPV tests), the effect of changes in disease prevalence on predictive values, possible alteration of disease process and the effect upon the cost-effectiveness of screening.

Ms Kerry-Ann O'Grady (Vaccine and Immunisation Research Group, Murdoch Childrens Research Institute and School of Population Health, University of Melbourne) described involvement in a quadrivalent HPV vaccine trial in Melbourne. The trial aimed to determine the immunogenicity, safety and end expiry specifications of the vaccine. The study recruited 150 adolescents through schools with study participation occurring at home visits. Sexual activity was an exclusion criterion and pregnancy testing occurred at every visit for all girls. Ms O'Grady discussed the challenges in the recruitment of the participants, particularly in relation to the sensitivity of the subject matter, privacy legislation, timing of the study in the school year, busy families and refusals. Ethical issues which the investigators had to address through detailed guidelines, related to dealing with HPV positive serology at baseline, and actions if, during the study, there was disclosure of abuse or sexual activity, or a positive pregnancy test. Future needs in relation to HPV vaccine trials identified included a need to address privacy laws, gain a greater understanding of the likely acceptability of these vaccines to the community and consider alternative implementation strategies for trials in this age group.

Determining the priorities

Small group discussions were held to determine future priorities for HPV research in Australia as it pertains to vaccination. Priorities determined were:

1. adequate local knowledge of age/sex/type specific burden of disease. This should particularly focus on women most at risk such as Indigenous women and women from certain ethnic groups and include the burden of disease from genital warts.

2. data collection for, and undertaking of, health economic analyses that would inform decisions about population use of HPV vaccines and about the target groups for vaccination (especially in relation to the impact on screening programs); and
3. the need to develop an understanding of communication and implementation issues relating to HPV immunisation of adolescents and the general population.

The key recommendations for future initiatives in HPV research were:

1. epidemiological data collection is a priority using modern assays/genotyping and representative sampling, preferably across Australia, but if necessary focusing on those groups with potentially most to benefit from vaccination (high risk groups).
2. measure type specific HPV prevalence now, and after vaccine introduction (replacement studies);
3. assess current burden of illness and costs from cervical cancer, genital warts and other HPV related diseases.
4. plan for impact of vaccination on cervical screening and disease burden including modelling. Start developing epidemiological and health economic models to assess where we should be focusing on getting 'harder' Australian data.
5. a focus on collaboration to ensure securement and efficient expenditure of adequate research funding;
6. education/communication strategy research;
7. utilise standardised serological test interpretation once available; and
8. ongoing assessment of the importance of sequence variation in L1 HPV 16 and 18.

The group plans to reconvene in 2004, following the February International Papillomavirus Conference, to discuss ongoing research, results and collaborations.

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In attendance at the meeting were:

Mr Brian Brestovac, Division of Microbiology and Infectious Diseases, PathCentre (The Western Australian Centre for Pathology and Medical Research)

Professor Yvonne Cossart, Department of Infectious Diseases and Immunology, University of Sydney

Dr Elizabeth Davey and Ms Petra Macaskill, School of Public Health, University of Sydney

Professor Ian Frazer and Ms Olivia White, Centre for Immunology and Cancer Research, University of Queensland

Assoc. Professor Suzanne Garland and Dr Sepehr Tabrizi, Department of Microbiology and Infectious Diseases, Women's and Children's Hospital, Melbourne

Professor Lyn Gilbert, Centre for Infectious Diseases and Microbiology, Westmead Hospital

Ms Kerry Ann O'Grady, Vaccine and Immunisation Research Group, Murdoch Childrens Research Institute and the School of Population Health, University of Melbourne

Assoc. Professor Freddy Sitas, Research and Registers Division, The Cancer Council NSW

Dr Julia Brotherton, Professor Margaret Burgess and Assoc. Professor Peter McIntyre, National Centre for Immunisation Research and Surveillance

Dr John Anderson, Dr Lynne Conway, Dr Jane Greig and Dr Neil Formica, CSL Vaccines

Dr Damien Cramer, Ms Melanie Duiker and Dr Catherine Streeton, Glaxo SmithKline Biologicals

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