CSIRO PUBLISHING
www.publish.csiro.au/journals/sh
Review
Sexual Health, 2010, **7**, 310–319

Monitoring the control of human papillomavirus (HPV) infection and related diseases in Australia: towards a national HPV surveillance strategy

Julia M. L. Brotherton[A,B,H], *John M. Kaldor*[C] *and Suzanne M. Garland*[D,E,F,G]

[A]Victorian Cytology Service, PO Box 310, East Melbourne, Vic. 8002, Australia.
[B]National Centre for Immunisation Research and Surveillance, The Children's Hospital at Westmead, Discipline of Paediatrics and Child Health, School of Public Health, University of Sydney, Sydney, NSW 2006, Australia.
[C]National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, NSW 2010, Australia.
[D]Clinical Microbiology and Infectious Diseases, Royal Women's Hospital, Melbourne, Vic 3052, Australia.
[E]Department of Clinical Microbiology, Royal Children's Hospital, Melbourne, Vic. 3052, Australia.
[F]Faculty of Medicine, Dentistry and Health, Department of Obstetrics and Gynaecology, University of Melbourne, Melbourne, Vic. 3053, Australia.
[G]Murdoch Children's Research Institute, University of Melbourne, Melbourne, Vic. 3052, Australia.
[H]Corresponding author. Email: jbrother@vcs.org.au

Abstract. This paper describes a possible multifaceted approach to human papillomavirus (HPV) related surveillance in Australia following implementation of a national HPV vaccination program. We describe eight main components: monitoring of vaccine coverage, vaccine safety, type-specific HPV infection surveillance, cervical cytology (Pap screening) coverage and screen detected lesion prevalence, cervical cancer incidence and mortality, genital wart incidence, incidence of recurrent respiratory papillomatosis, and knowledge, attitudes and beliefs about HPV and HPV vaccination. Australia is well placed to monitor the impact of its HPV vaccination program as well as to measure vaccine effectiveness with existing HPV vaccines, cervical screening and cancer registries.

Additional keywords: cervical cancer, genital warts, Pap smears, recurrent respiratory papillomatosis, vaccination, vaccine safety.

Introduction

Australia was the first country to implement a fully government funded national population-based human papillomavirus (HPV) vaccination program to prevent cervical cancer. The National HPV Vaccination Program began in April 2007 and is an ongoing program for 12- to 13-year-old girls delivered in the first year of high school. The program also included a 2-year catch-up vaccination program, concluding in December 2009, for females aged 13–18 years, largely delivered in school-based programs, and for women aged 18 to 26 years, delivered through general practice (GP) and community-based immunisation providers. Detailed descriptions of the program are available elsewhere.[1,2] To date, the program has used the quadrivalent HPV vaccine, which was the only vaccine available at the time of program commencement, and which also provides protection against HPV types 6 and 11, which cause >90% of genital warts.

Australia has a very effective secondary prevention program for cervical cancer, the National Cervical Screening Program (NCSP). The NCSP provides organised cervical cytology screening through regular (2-yearly) Pap testing, for women aged 18 to 69 years and is monitored through state-based cervical cytology registers (which also record histology results for those biopsied). Current participation among the target age group is 61.5% every 2 years, with 86.4% 5-yearly participation.[3] Pap test screening is effective at preventing cervical cancer when used regularly, as it enables the early identification of cytological changes and the treatment of precancerous cervical lesions (high grade dysplasias) before invasive cancer develops. Between the commencement of the NCSP in 1991 and 2005, the incidence of cervical cancer in women of all ages decreased from 12.7 to 6.9 per 100 000 (age standardised to the Australian population).[3]

The introduction of prophylactic HPV vaccination is expected, in the long-term, to reduce the incidence of cervical cancer even further. By preventing vaccine-related HPV genotype transmission, vaccination should also reduce the incidence of high grade dysplastic and, to a lesser extent, low grade dysplastic cervical lesions. With sufficient vaccine

10.1071/SH09137 1448-5028/10/030310

coverage by either of the vaccines currently available, a reduction in other HPV-related anogenital and HPV-associated oropharyngeal disease is also anticipated, while the use of the quadrivalent vaccine should also result in a reduction in genital warts and recurrent respiratory papillomatosis (RRP), both largely caused by HPV types 6 and 11 (HPV-6 and HPV-11).

This paper describes a potential multifaceted approach to monitor the control of HPV and related diseases in Australia, which is in a unique position to capitalise on the combination of high quadrivalent HPV vaccine uptake, across a wide age range, alongside the existence of a vaccine register, cervical cytology registries and cancer registries, and in the context of a mature and successful national cervical cytology screening program. Cervical screening starts at a relatively young age in Australia (from age 18) and there was an immediate overlap in the age groups targeted for HPV vaccination and for cervical screening. With time, a larger proportion of cohorts will have been vaccinated before sexual debut. Although early assessment is possible in Australia, the full impact of vaccination on incident HPV infection and related cervical disease will not emerge for at least 5 years, at which time this cohort will enter screening. Other developed countries have various combinations of Australia's relevant public health infrastructure (e.g. Nordic countries have linked registry systems but do not have a high uptake vaccination program with a catch-up component in place yet; the UK has a high uptake of the bivalent vaccine in their primary target cohort, with cervical and cancer registries in a mature screening program, but no national vaccine register; and the USA has national HPV vaccine recommendations but not a high population coverage as yet, with cancer registries in place but not cervical cytology registries.) The various components of HPV-related surveillance in the USA have recently been described by Markowitz *et al*.[4] We believe Australia is in a position to assess various components of a comprehensive HPV vaccination program in a timely manner and more feasibly than many other developed countries. While much of this work is already underway, formally implementing such a comprehensive surveillance system requires political will and would necessarily involve wider consultations with stakeholders.

Vaccine program monitoring: background and rationale

Literally millions of lives have been saved by immunisations for various infectious diseases. However, at the start of any (and every) immunisation program, there is uncertainty. Key questions include:

1. Who, and how many, will be successfully vaccinated? (vaccination coverage)
2. Will there be any unexpected side effects or rare effects not detected in the clinical trials? (adverse events following immunisation)
3. Will the vaccine prevent the disease in the real world? (vaccine effectiveness)

We address this uncertainty through systematic monitoring of the program, which is an example of public health surveillance and an essential component of any immunisation program. Public health surveillance has been defined as '*the ongoing*, *systematic collection*, *analysis*, *interpretation and dissemination of data regarding a health-related event for use in public health action to reduce morbidity and mortality and improve health*'.[5] As highlighted by this definition, a critical aspect in understanding the role of post-vaccination surveillance systems is to appreciate that the information they collect is only of value if it is analysed, reported and used to improve the program in a timely way.

HPV surveillance and vaccine program monitoring: some unique challenges

HPV infection and related diseases pose unique challenges for surveillance systems. Some of these relate to the nature of HPV infection and related diseases, the long time interval between vaccination of pre-adolescent cohorts and the age at which cervical cancer typically develops, and the lack of standardised HPV testing methods.

In relation to vaccination coverage, the three-dose schedule used for both vaccines may not only be challenging to implement but requires an ability to link individual vaccination episodes to the one person to estimate coverage accurately. In addition, the natural history of the development of cervical cancer precursor lesions and cervical cancers means that records of an individual's HPV vaccination status should be kept long-term. The World Health Organization (WHO) recommends that '*After HPV vaccination programs are introduced*, *coverage by individual*, *age and district should be measured and records retained for the long-term*'.[6]

The safety of HPV vaccines, like all newly introduced vaccines, should be monitored, especially in the first decade of use, and they can readily be added to existing vaccine safety monitoring systems and should be.[6] Coincident health events following HPV vaccination can be expected when three doses are given to a population of young women, in whom incident disease profiles are quite different to those seen in childhood.[7]Thus important challenges exist relating to the inevitable need for rapid communication and investigation when vaccine safety concerns arise.

In relation to disease incidence, because HPV infection is generally an asymptomatic, transient and untreatable infection that is highly prevalent, traditional models of infectious disease notification from clinicians and laboratories, as used, for example, for the surveillance of measles or meningitis, are not appropriate or feasible. HPV vaccines are prophylactic only (i.e. they prevent infection in unexposed vaccinees, but do not treat prevalent infection; for this reason, they are targeted primarily at girls aged 12–13 who have not yet started sexual activity). However, they have been delivered in Australia and elsewhere to many women who were already sexually active and who therefore may have already been infected. This issue makes surveillance for possible vaccine failure (i.e. disease occurrence despite vaccination) extremely challenging. Moreover, HPV infection status is not assessed before vaccination so the baseline HPV exposure status of individuals that have been vaccinated is unknown and unmeasurable. For young women in Australia's catch-up cohort who develop Pap abnormalities related to HPV types targeted by the vaccine, it is far more

likely that these occurrences will not represent vaccine failure in any traditional sense, but will be caused by pre-existing prevalent infection, i.e. failure to vaccinate before infection. The consequences of vaccination in the presence of prevalent infection will become less of an issue as cohorts vaccinated in preadolescence enter screening, but, in the interim, this could potentially undermine confidence in the vaccine when vaccinated women develop Pap abnormalities.[8] HPV vaccines are intended to prevent infection with specific HPV types (types 16 and 18 for both vaccines, and additionally types 6 and 11 for the quadrivalent vaccine), from among the ~40 types that may infect, and frequently co-infect, the genital tract. Thus monitoring of HPV infection endpoints needs to include type-specific data. WHO recommends that countries consider '*establishing sentinel surveillance to monitor the impact of vaccination on the prevalence of HPV types*, *the incidence of cervical abnormalities and precancerous lesions*, *the incidence and mortality of invasive cancer*, *and the incidence of anogenital warts*'.[6] Further guidance from WHO about such surveillance, with a focus on low and middle income countries, is under development.[9]

The WHO Global HPV Labnet was established in recognition of the lack of standard methods for HPV typing and serology. Recently, international standards for HPV-16 and -18 have been developed so that various assays can be compared.[10] The network has regional reference laboratories which offer expertise, training and assistance with HPV detection and typing for HPV surveillance. Because HPV DNA testing is non-standardised, it is strongly recommended that those developing HPV surveillance systems avail themselves of this expertise in order to ensure quality results and comparable use of assays across regions.

A possible approach to monitoring the control of HPV and related diseases in Australia

There are eight key areas requiring development in order to monitor the impact of the HPV vaccination program in Australia comprehensively. Table 1 summarises the proposed objectives, key indicators and the current status in relation to both current capacity and work yet to be done in order to monitor that objective. The rationales for each of the eight objectives are discussed below.

Assess age-specific HPV vaccination coverage achieved in the ongoing 12–13-year-old program and the catch-up program

Vaccination coverage indicates how successfully the program delivers the vaccine to the target group(s) and, therefore, whether strategies are required to improve coverage further. It allows identification of groups or areas with lower vaccine uptake, which can assist with targeted immunisation efforts. The HPV Vaccination Program will fail in its objective of reducing cervical cancer if it fails to vaccinate young girls who are part of the demographic groups which include those women who currently develop cervical cancer in Australia. These are predominantly women who do not fully participate in the Cervical Screening Program and include women who: are Indigenous, are from certain culturally and linguistically diverse groups, live in rural or remote areas, and live in areas of low socioeconomic status, especially those with high population growth. That is, high vaccination coverage in these population groups, in particular, is required for success. Coverage in these groups should be assessed early, regularly and throughout the life of the program. Assessment of the adequacy of vaccine coverage achieved can be assisted by mathematical modelling, and models for the Australian setting continue to be refined.[11,12]

Because the target group for the HPV vaccination program fell outside the age range of the Australian Childhood Immunisation Register, a specific strategy to estimate age-specific vaccine coverage from the program was required. The National HPV Vaccination Program Register (NHVPR), which is owned by the Australian Government Department of Health and Ageing and operated by the Victorian Cytology Service, was established to meet this need, as well as to assist in administering the program and for monitoring and evaluation (for details about the NHVPR, please see the accompanying paper[13]). The NHVPR receives individual notifications of HPV vaccination doses administered from all types of immunisation providers, including the school-based programs. Vaccine recipients give consent for their records to be provided to the NHVPR and to be used for program monitoring. Population-based estimates (from the Australian Bureau of Statistics or, for school enrolments, from the state-based education authorities) are used as denominators when calculating coverage. It will be important, however, to validate the registry data, particularly in relation to potential under notification, through assessment of dose distribution data and population-based surveys. The registry will analyse coverage by geographical area of residence to indicate vaccine coverage in areas of lower socioeconomic status, rural and remote regions, and areas with high proportions of residents from culturally and linguistically diverse backgrounds. The NHVPR also records Indigenous status. The NHVPR will formally publish an annual vaccination coverage report, with real-time coverage reports available throughout the year to registered immunisation providers, program administrators and state health departments via the secure web-portal.

Monitor vaccine safety

An adverse event following immunisation (AEFI) is an unwanted or unexpected event occurring after the administration of a vaccine(s).[14] It may be caused by the vaccine or the vaccination process, or may occur by chance after vaccination. It is important to closely monitor AEFIs after the introduction of new vaccines into population-based immunisation programs. It is of particular importance to monitor the safety profile of HPV vaccines, as they are new vaccines and are given to an older population group than most childhood vaccines, where a different range of co-incidental events may be experienced.[7] The aim of AEFI surveillance is to monitor vaccine and immunisation program safety, and to detect population-specific, rare, late onset or unexpected adverse events.[15]

In Australia, AEFIs are notified to the office of Medicines Safety Monitoring of the Therapeutic Goods Administration

Table 1. HPV-related surveillance objectives for Australia, proposed indicators and current implementation status

Surveillance objective	Proposed key indicators	Current status
1. Assess age-specific HPV vaccination coverage achieved in the ongoing 12–13-year-old program and the catch-up program	Coverage indicators are to be reported by dose number and at national, state and regional levels • Immunisation coverage in girls in the first year of high school (12–13 years) (ongoing). • Immunisation coverage in each school year cohort for the 2 years of the catch-up program. • Immunisation coverage in women aged 18–21 years, and 22–26 years for the 2 years of the catch-up program. • Immunisation coverage in Indigenous women. • Immunisation coverage in women residing in areas of low socioeconomic status, and in rural or remote areas.	• NHVPR established. • All catch up program data due to NHVPR by mid-2010. • Interim coverage data published.
2. Monitor vaccine safety	• An annual report of AEFI with HPV vaccines should be published.	• HPV vaccine included in annual AEFI report.[18] • Regular updates are provided on the Therapeutic Goods Administration website (http://www.tga.gov.au/alerts/medicines/gardasil.htm; verified June 2010).
3. Monitor the prevalence of HPV genotypes in: the general female population; high grade cervical dysplastic lesions; and cervical cancers	An annual report of the HPV type specific surveillance system should be published and report: • Prevalence of HPV by type in a sentinel sample of women with normal Pap tests (±women with Pap tests showing low grade cytology). • Prevalence of HPV by type in a sentinel sample of women with histologically proven CIN 3. • Prevalence of HPV by type in cervical cancer specimens. For each of the above indicators, analysis should include: • comparisons over time and with sufficient power to detect significant changes. • analysis by age cohort, vaccination status, Indigenous status and geographical area. • an estimate of the proportion attributable to vaccine preventable and non-vaccine preventable HPV types. • For cervical cancers, analysis should also include the number of cancer specimens typed for HPV as a proportion of all cancers diagnosed (aim for complete capture) and analysis by histological type.	No surveillance yet in place due to lack of funding commitment although baseline data are available. The short term priority is immediate monitoring of cervical HPV prevalence in young women post the implementation of the vaccination program. Funding will be required in the near future to commence CIN3 surveillance. Ideally cancer typing should commence in the next five years to provide sufficient baseline data for future comparisons.
4. Continue to monitor the uptake of cervical cytology screening in the eligible population and the prevalence of screen detected cervical abnormalities[A]	• 2, 3 and 5-year participation rates for cervical screening – the percentage of women screened in a 2, 3 or 5-year period for women aged 20 years and over and for the target screening age group 20–69 years. • Participation by region – the percentage of women screened during a 2-year period by geographic region of residence for women aged 20 years and over and for the target screening age group 20–69 years. • Participation by socioeconomic status – the percentage of women screened during a 2-year period by socioeconomic status of area of residence for women aged 20 years and over and for the target screening age group 20–69 years. • Participation by vaccination status – 2, 3 and 5-year participation rates for vaccinated women as compared to unvaccinated women in age eligible vaccine cohorts. • Early re-screening – the proportion of women re-screened, by number of re-screens, during a 21-month period following a normal Pap test for women in the target screening age group 20–69 years. • Low-grade abnormality detection – detection rate of low-grade intraepithelial abnormality on cytology per 1000 women screened in a 12-month	• Annual report 'Cervical screening in Australia' published by the Australian Institute of Health and Welfare includes existing national program indicators such as program participation, early re-screening, and high grade abnormality detection.[3] • Methods for ascertaining and monitoring cervical screening participation by Indigenous women and women from culturally and linguistically diverse backgrounds need to be developed. • Monitoring of rates of low grade Pap abnormalities can currently be undertaken only using State based registers. New national indicators, including a new cytology performance indicator, have been developed and will be included for the first time in the 2008–2009. • Cervical Screening in Australia report.

	period for women aged 20 years and over and for the target screening age group 20–69 years. • High-grade abnormality detection – detection rate of histologically verified high-grade intraepithelial abnormalities per 1000 women screened in a 12-month period for women aged 20 years and over and for the target screening age group 20–69 years. • Low-grade abnormality detection rates by vaccination status – detection rate of low-grade intraepithelial abnormality on cytology per 1000 women screened in a 12-month period for vaccinated women as compared to unvaccinated women in age eligible vaccine cohorts. • High-grade abnormality detection rates by vaccination status – detection rate histologically verified high-grade intraepithelial abnormalities per 1000 women screened in a 12-month period for vaccinated women as compared to unvaccinated women in age eligible vaccine cohorts.	• Calculation of participation and abnormality detection rates by vaccination status will require data linkage between the NHVPR and Pap test Registers. Whilst the NHVPR is underpinned by legislation enabling such linkage, the legality of such linkage to each of the State based Pap test registers requires assessment. To date, one State has amended Pap test register legislation.
5. Continue to monitor cervical cancer incidence and mortality	• Incidence rate of micro-invasive squamous cell cervical carcinoma per 100 000 estimated resident female population in a 12-month period for women of all ages and for the target screening age group 20–69 years. • Incidence rate of squamous, adenocarcinoma, adenosquamous and other cervical cancer (micro-invasive and invasive) per 100 000 estimated resident female population in a 12-month period for women of all ages and for the target screening age group 20–69 years. • Incidence rate of cervical cancer per 100 000 estimated resident female population in a 4-year period by geographic region for women of all ages and for the target screening age group 20–69 years. • Mortality rate for cervical cancer per 100 000 estimated resident female population in a 12-month period for women of all ages and for the target screening age group 20–69 years. • Mortality rate for cervical cancer per 100 000 estimated resident female population in a 4-year period by geographic region for women of all ages and for the target screening age group 20–69 years. • Mortality rate for cervical cancer per 100 000 estimated resident female population in a 4-year period by Indigenous status for women of all ages and for the target screening age group 20–69 years.	• Routine indicators and reports established under the National Cervical Screening Program are suitable and ongoing.[13] • Measurement of these indicators by vaccination status will occur in the future through individual record data linkage with vaccination data held on the NHVPR.
6. Monitor the incidence of genital warts	• Trends in genital warts incidence in clinic populations by age, sex and sexual orientation over time (with reference to baseline and historical clinic data prior to the National HPV Vaccination Program).	• No nationally funded surveillance program. • Multi-site pilot project funded by industry.[37]
7. Monitor the incidence of recurrent respiratory papillomatosis	• Trends in recurrent respiratory papillomatosis (RRP) incidence over time.	• No nationally funded surveillance program or RRP register. • Un funded pilot study of baseline data, ICD coding and willingness of treating surgeons to participate in future surveillance undertaken.[38]
8. Monitor knowledge, attitudes and beliefs about HPV and HPV vaccination	• Report on trends in the degree of community support for HPV vaccine and participation in screening programs in Australia.	• In 2009, VCS convened an expert group to develop modules of HPV CATI questions relevant to the Australian setting for use by researchers. These are available on request from jbrother@vcs.org.au. • No nationally funded survey mechanism to date.

[A]For all rates, absolute numbers of Pap tests and the specified outcome of interest are also reported by age and over time.

(TGA) by state and territory health departments, health professionals, vaccine manufacturers and individuals. This form of AEFI surveillance is passive rather than active, being reliant on provider reporting rather than seeking out occurrences of reactions. Provider reports cover both immediate and longer term health events that are observed following receipt of the vaccine. Typically, passive surveillance is more likely to detect more serious events than minor problems and reporting rates tend to increase early after vaccine introduction and to wane over time as providers become familiar with common AEFIs (the Weber effect). There is a large degree of variation in reporting AEFI rates between jurisdictions. The limitations of the current national AEFI surveillance mechanisms in Australia have been well described.[16] As detailed by Gold *et al*.,[17] no changes to AEFI surveillance mechanisms were made for HPV vaccine surveillance. The HPV vaccine is now included in annual reports of the AEFI surveillance system.[18] The National HPV Vaccination Program reinforces the need to continue to work towards a more cohesive and consistent approach to AEFI surveillance across Australia.

Monitor the prevalence of HPV genotypes in: the general female population, high grade cervical dysplastic lesions and cervical cancers

Genotype-specific HPV surveillance of prevalent cervical infections, confirmed high grade cervical dysplastic lesions and cancers is valuable for three main reasons:

1. To monitor changes in the prevalence of both the high-risk (HPV-16 and -18) and low-risk (HPV-6 and -11) genotypes included in the quadrivalent HPV vaccine currently used in the national HPV vaccination program. This will assess the effectiveness of the vaccination program in preventing the targeted HPV infections and disease.
2. To monitor changes in the prevalence of non-vaccine genotypes and to evaluate what proportion of the disease burden is vaccine preventable over time. This will assess the effectiveness of the vaccination program in providing cross-protection against infection and disease due to non-vaccine but phylogenetically related HPV genotypes. It is also important to guide further vaccine development, in which it is expected that antigens for additional genotypes will be included.
3. To monitor for potential genotype replacement, where a previously uncommon non-vaccine genotype becomes more common, 'replacing' the common HPV genotypes targeted by the vaccine. Although this occurrence is felt to be ecologically unlikely, it is important that at least one country with high vaccine coverage monitors closely for this event.

In order to achieve these objectives, as outlined in Table 1, HPV genotyping needs to occur on:

a) normal cervical and low grade abnormality cervical smears,
b) biopsy specimens from cervical intraepithelial neoplasia 3 (CIN3), and
c) cervical cancers.

HPV DNA testing is not currently used for screening in Australia. There is no routine process for genotyping of the HPV found in normal or abnormal cervical smears in Australia. HPV prevalence data collected before the introduction of HPV vaccination in a sample of sexually active women is available from a research study (WHINURS: Women, HPV, Indigenous, Non-Indigenous, Urban, Rural Study), in which consenting women aged 15 to 70 (the majority aged 18 to 40) agreed to have their routine cervical sample(s) tested for type-specific HPV DNA. WHINURS recruited in all Australian jurisdictions from healthy women presenting for cervical cytology (Pap) screening to Family Planning Clinics, Well Women's Clinics and Indigenous Health Centres. Over 2500 women were recruited, including 700 Indigenous participants.[19] A suitable method of undertaking type-specific surveillance in normal cervical smears (as Pap testing starts at age 18 in Australia and women in the vaccination catch-up cohorts are already attending screening) would be to use the sentinel site model and methodology used in WHINURS to prospectively collect suitable specimens for HPV genotyping, with each site providing a certain number of specimens per year on an ongoing basis. Although the women at these sentinel sites may not necessarily be representative of all Australian women, monitoring rates of change in HPV prevalence among women attending these sites will allow an assessment of vaccine impact, as long as the source population and methods remain consistent over time. Demographic details and sexual history information will allow the degree of representativeness of women providing samples at the sentinel sites to be assessed. Should high risk HPV DNA testing become part of the primary screening pathway in Australia, monitoring will be facilitated, especially if the testing used is type-specific.

There is currently no routine or ongoing type-specific HPV typing of high grade cervical lesions in Australia. While high risk HPV testing is recommended in Australia as a test of cure following treatment of high grade lesions, these specimens are taken after treatment, are not biopsy specimens and usually do not determine the infecting type. Australian HPV type distribution data in high grade lesions detected across the age range of women attending screening, sampled before the HPV vaccination program, are available from research studies.[20,21]

With unlimited resources, HPV genotype surveillance of both CIN2 and CIN3 high grade lesions could be undertaken, with analysis by grade of lesion. However, it is now thought that CIN2 is really a mixture of lesions, some of which represent acute HPV infection with dysplastic cellular change and others which are true high grade dysplasias, the true precursor lesions to cancer.[22] This is borne out by the fact that non-oncogenic HPV infections are capable of producing CIN2 and also by the greater likelihood of progression to cancer among women treated for CIN3 compared with those treated for CIN2 (odds ratio = 4.0 at one year).[23] Consequently, a focus on genotype surveillance of CIN3 lesions would be most appropriate and the highest priority. Concentrating only on typing of CIN3 lesions will ensure adequate numbers of specimens are typed, rather than obtaining a dataset in which CIN2 specimens will predominate. Due to the immediate

intersection of vaccinated cohorts and cervical screening eligibility in Australia, the focus in the short term will be on screen-detected abnormalities in young women.

A new protocol is required for the collection of a sample of cervical biopsies from CIN3 lesions for HPV genotype testing. As following up screen-detected high grade squamous intraepithelial lesions requires colposcopic follow-up and cervical biopsy of abnormal areas, sentinel site gynaecologists and their histopathology laboratories could be recruited to forward a sample of CIN3 lesion specimens in paraffin block to the WHO regional reference laboratory or a local WHO-accredited laboratory for HPV detection and typing. Consideration would have to be given to logistics, ethical approval and patient consent. Alternatively, with appropriate legislative or regulatory amendments such surveillance could become part of one or more Pap test registers' mandates and, in this case, may be able to occur without individual consent for HPV DNA testing. Ideally, the register could randomly select from notifications of CIN3 and routinely request the notifying laboratory to prepare and forward a section of the diagnostic biopsy specimen to a reference laboratory for HPV typing, with the register recording and monitoring the results of such typing over time. Developing such a system would require appropriate funding and consultation.

Cervical cancers in Australia are not routinely tested for HPV genotype. Australian data indicate that 70–80% of cancers contain HPV-16 or -18 DNA.[24] As the number of cervical cancers in Australia is small, and this number should decrease following the introduction of the HPV vaccination program, all cancers should be tested for all HPV genotypes. It would be logical to record this data on the existing state-based cancer registries. Data on vaccination status from the NHVPR should be linked to each cancer record, including the HPV genotype information. The NHVPR has been set up through legislation to allow such data linkages with individual consent given. In the case of cervical cancers, which are rare in Australia, this linkage would probably occur through individual record matching by registry staff with transfer of vaccination status to the cancer registry record. Indigenous status of women diagnosed with cervical cancer should be obtained from cancer registries, the NHVPR or other sources to detect any differences in HPV types found in cervical cancer by Indigenous status.

The logistics of ensuring HPV testing of all cervical cancer specimens would involve all pathology laboratories that currently perform cervical histology. Reporting laboratories would need to be requested to forward a paraffin block containing the cancer to an accredited WHO laboratory for HPV detection and typing. Initial scoping and communication should occur with the state or territory cancer registries in order to streamline the addition of typing information into existing processes for the reporting of cervical cancer to the registers. Implementation via quality control and quality assurance programs such as the Quality Use of Pathology Program, an Australian Government program, which aims to achieve improvements in the use of pathology in health care through better practice initiatives, could be explored in the first instance.

Continue to monitor the uptake of cervical cytology screening in the eligible population and the prevalence of screen detected cervical abnormalities

One of the major impacts expected where HPV vaccination is successfully implemented is a reduction in cervical abnormalities (both high and low grade) caused by HPV types covered by the vaccine. International data indicate that ~55% of high grade cervical abnormalities are associated with HPV-16 or -18.[25] Available Australian data suggest that 45% of high grade lesions are associated with HPV-16 or -18.[20,21] Of low grade cervical abnormalities, 25% are associated with HPV-16 or -18.[26] A further proportion of cervical abnormalities are associated with types against which HPV vaccines may provide some degree of cross-protection.

Opt-off cervical screening registers operate in each State and Territory (i.e. women who do not wish their details and results to be included on the register can notify the register directly or via informing their provider at the time of Pap test collection. Less than 1% of women choose to opt off).[27] These registers are not population-based but use Australian Bureau of Statistics population estimates, adjusted for hysterectomy rates, to determine the denominator for calculating participation rates. The registers operate to collect screening histories of individual women, including screen-detected abnormalities; to send reminders to women apparently overdue for routine screening; to provide a follow-up safety net function for women who have abnormal Pap test results; and to provide the laboratory or clinician with the results of previous abnormal smears, so that a more detailed evaluation of the present smear can be done if necessary. The registers also support monitoring of laboratory quality, and provide data for analysis and consideration in policy development for the National Cervical Screening Program.

The extent of the impact of HPV vaccination on cervical abnormalities should increase as the cohort of vaccinated women grows older and increasing numbers of them become the target population for the screening program. Thus, monitoring the absolute numbers of abnormalities (against the total number of Pap tests collected) detected both cytologically and histologically (and in conjunction with information provided by sentinel surveillance of HPV types present in such lesions) is an important outcome indicator of the program's effectiveness. This is important for both high grade and low grade abnormalities. Of note, the number of cytologically detected low grade abnormalities is not currently reported as one of the national cervical screening program monitoring indicators. At present only histologically verified CIN1 lesions are reported nationally, despite a first low grade smear result not necessarily being an indication for biopsy. For national surveillance, the total number of Pap smears classified as low grade is required.[28] The National Cervical Screening Program has developed new performance indicators for national monitoring by the Australian Institute of Health and Welfare. These include a new cytology performance indicator that will allow the annual reporting of squamous and endocervical cytology result categories by year and by age. New performance indicators are expected to appear for the first time in 'Cervical screening in Australia 2008–2009' (pers. comm.,

Dr Alison Budd, Cancer & Screening Unit, Australian Institute of Health and Welfare, April 2010).

Interpretation of the numbers and rates of cervical abnormalities over time relies critically on the context in which these abnormalities are diagnosed (i.e. the screening program) and valid information on vaccination status. It is only with concomitant information about trends in screening coverage, age of participants and rates of follow-up that these trends can be interpreted. National reports of these indicators (described in Table 1) are published annually,[3] in addition to regular reports from each of the State and Territory cervical cytology registries. Data describing the characteristics of sexual behaviour in the population, such as age at first intercourse and number of partners, will also be important to monitor as potentially confounding variables. Should Australia move to screening using HPV DNA testing as the first step in the screening pathway, absolute numbers of CIN3 lesions detected and treated by the screening program could still be compared with historical data, as could cancer incidence and mortality.

Through future data linkage between the Pap test registers and the national HPV vaccine register (enabled by the individual consent obtained by the vaccination register), Australia will be able to monitor Pap outcomes not only at an ecological level but also through individually linked datasets that ascertain the vaccination status of screened women, and will thus be able to track trends in participation and Pap results in both vaccinated and unvaccinated women.

Continue to monitor cervical cancer incidence and mortality

Prevention of cervical cancer is the major aim of population-based HPV vaccination programs. Although the impact of vaccination on preventing cervical cancer will not be realised for several decades, given the natural history of the disease, continued high quality surveillance of cervical cancer incidence is required.

All Australian states and territories operate cancer registries that are mandated under the various state and territory reporting requirements. Therefore, national, State and Territory reporting of cervical cancer incidence and mortality is currently comprehensive, with annual publication of cervical cancer incidence and mortality data[3]. Existing indicators are described in Table 1.

As described under Objective 3, linkage of HPV vaccination registry data with cancer registry records at an individual level will be possible in the future due to the obtaining of consent for such linkage at the time of HPV vaccination.

Monitor the incidence of genital warts

At least 90% of genital warts are caused by two low-risk HPV types, HPV-6 and HPV-11, both of which are targeted by the quadrivalent vaccine that has been used in the national HPV vaccine program to date.[29] Based on efficacy data from clinical trials,[30] the vaccination program can be expected, therefore, to have a large impact on the incidence of genital warts if adequate vaccine coverage is achieved. Because of the short lead-time (months) between HPV infection with types 6 and 11 and genital warts, decreases in incidence should occur rapidly following the vaccination program. This is in marked contrast to cervical cancer rates, which will take decades to fall. Therefore, genital warts are a useful and early marker of the impact of the vaccination program on HPV infection rates at a population level.

There was no pre-existing system of genital wart surveillance in Australia before vaccine introduction. Estimates of the disease burden due to genital warts in Australia are potentially available through hospitalisation data (day stay for surgery), sexual health clinics (although this is not routinely reported or collected centrally) and from sentinel general practices (GPs) through the Bettering the Evaluation and Care of Health (BEACH) program. Genital warts are usually diagnosed clinically, without confirmatory pathology, so pathology databases cannot be used as a surveillance mechanism.

Sentinel surveillance would provide the most efficient means of surveillance for genital warts. Sexual health clinics, which serve young sexually active people, of whom ~1 in 10 is currently diagnosed with genital warts, would be an appropriate site for genital wart surveillance. Indeed, the first population-based evidence of vaccine effectiveness in women (as well as males) aged <27 years has been observed through such monitoring at a single large sexual health clinic in Melbourne, irrespective of vaccine history, clearly indicating the feasibility of such surveillance and the short time taken to impact upon this disease end point with sufficient coverage.[31]

Monitor the incidence of recurrent respiratory papillomatosis

RRP is a disease causing recurrent benign growths in the airways that usually require repeated surgical treatments, and is associated with high morbidity and occasionally death.[32] There are two forms, one seen in children and the other in adults. Two low-risk HPV genotypes, HPV-6 and HPV-11, are found in almost 100% of RRP lesions.[32] Although rare (incidence: 1–4 per 100 000), epidemiologic data suggests that children delivered vaginally to young mothers with active genital warts are at greater risk of the condition. As both HPV-6 and HPV-11 are targeted by the quadrivalent vaccine used in the National HPV Vaccination Program, the rate of HPV-6 and -11 infection and genital warts in women of child-bearing age should decrease over time. This should reduce the potential for vertical transmission of HPV-6 and -11 and thus RRP will become a vaccine preventable disease over time. An impact upon juvenile onset RRP (JORRP) incidence, particularly from the catch-up program that vaccinated females of reproductive age, may be observed relatively rapidly.

There is currently no routine surveillance of RRP in Australia. The Australian Paediatric Surveillance Unit (APSU) is designed to undertake specific surveillance of rare childhood diseases and would be well placed to coordinate this initiative. However, as JORPP cases appear to be almost entirely identified and followed through a small number of clinics nationally, it is likely to be more efficient for the APSU to liaise directly with these clinicians to support data collection and other relevant activities rather than using their normal

ascertainment mechanisms, which seek monthly reporting of cases from all paediatricians nationally.

Monitor knowledge, attitudes and beliefs about HPV and HPV vaccination

Knowledge, attitudes and beliefs about HPV infection and HPV vaccination may impact on the success of the HPV vaccination program and on the participation rates in cervical screening.

Uptake of the HPV vaccine may be influenced by attitudes of vaccine providers and those at-risk of infection or their parents.[33,34] Physician and parental attitudes to HPV vaccines may differ from their attitudes to other routine childhood vaccines for many reasons, including because the vaccine prevents a sexually transmissible infection.[35] Strong support from health care providers and from professional organisations is essential for fostering the acceptability and uptake of HPV vaccines. For school-based programs, appropriately targeted information and support from education authorities will be important contextual factors.[36] Doubt about a vaccine can affect vaccination coverage rates achieved through immunisation programs. For instance, parental concerns over the sexual implications of the HPV vaccination may reduce uptake of the vaccine, particularly where parents consider their children to be at low risk of acquiring infection in the immediate future. Publicity about adverse events associated with the vaccine can erode confidence in its safety and reduce uptake, especially in situations where the risk of disease is perceived to be low.

Screening participation may be impacted if vaccinated women believe the vaccine provides sufficient protection for them to no longer need to undergo regular screening.

Regular monitoring of the knowledge, attitudes and beliefs about HPV infection and vaccination among immunisation providers, parents and young women could assist in developing immunisation and cervical screening program responses, such as revised educational and promotional materials, to ensure a continued high uptake of the vaccine and participation in screening. This monitoring would be best undertaken by the incorporation of a small set of core questions into relevant existing surveys rather than undertaking specific stand-alone surveillance.

Expanded qualitative research into knowledge, attitudes and beliefs should be undertaken if there is a significant fall in uptake of HPV vaccination or in participation in the screening program.

Summary

Australia has an outstanding infrastructure, such as the NHVPR, Pap test registers and cancer registries, which will be used for monitoring the impact of the HPV vaccination program. Coupled with the scale and success of the national HPV vaccination program to date, a comprehensive HPV-related surveillance program must now urgently be put into place. As summarised in Table 1, a national commitment to developing and resourcing type-specific HPV surveillance, genital wart surveillance, RRP surveillance and monitoring cervical cytology screening participation amongst Indigenous women are outstanding issues. Should the HPV vaccination program be expanded in the future to include males, such a surveillance approach could readily accommodate the surveillance of vaccine coverage, vaccine safety, genital wart incidence and HPV-related cancers in males.

Funding

No specific funding was received for the development of this paper.

Conflicts of interest

JMLB was an investigator on an investigator-driven study of HPV prevalence in Australia that received partial equal and unrestricted grant funding from CSL Ltd and GlaxoSmithKline (GSK). She was also an investigator on a serosurvey of HPV antibodies in Australia that received funding for the laboratory testing component from CSL Ltd.

JMK is a co-investigator on a research project that has received support from Merck and CSL Ltd through the provision of the HPV vaccine (Gardasil).

SMG has received advisory board fees and grant support from CSL and GSK, and lecture fees from Merck and GSK. She has received funding through her institution to conduct HPV vaccine studies for MSD and GSK. SMG is a member of the Merck Global Advisory Board as well as the Merck Scientific Advisory Committee for HPV prophylactic vaccines.

Acknowledgements

We would like to acknowledge the intellectual contribution to the ideas contained in this paper made by the following individuals, with whom we have discussed many of the issues in this paper: Dr Rosemary Lester, Dr Shelley Deeks, Dr Bronwen Harvey, Dr Vicki Krause, Professor Peter McIntyre, Associate Professor Marion Saville, Dr Christine Selvey and Dr Rosalind Webby.

References

1 Leask J, Jackson C, Trevena L, McCaffery K, Brotherton J. Implementation of the Australian HPV vaccination program for adult women: qualitative key informant interviews. *Vaccine* 2009; 27: 5505–12. doi:10.1016/j.vaccine.2009.06.102

2 Garland SM, Brotherton JML, Skinner SR, Pitts M, Saville M, Mola G, *et al*. Human papillomavirus and cervical cancer in Australasia and Oceania: risk-factors, epidemiology and prevention. *Vaccine* 2008; 26: M80–8. doi:10.1016/j.vaccine.2008.05.041

3 AIHW. Cervical screening in Australia 2006–2007. Cancer series No. 47. Cat. No. CAN43. Canberra: AIHW; 2009.

4 Markowitz LE, Hariri S, Unger ER, Saraiya M, Datta SD, Dunne EF. Post-licensure monitoring of HPV vaccine in the United States. *Vaccine* 2010; in press. doi:10.1016/j.vaccine.2010.02.019

5 CDC. Updated guidelines for evaluating public health surveillance systems. *MMWR Recomm Rep* 2001; 50: 1–35. RR13

6 World Health Organization. Human papillomavirus vaccines WHO position paper. *Wkly Epidemiol Rec* 2009; 84: 118–31.

7 Siegrist C, Lewis E, Eskola J, Evans S, Black S. Human papilloma virus immunization in adolescent and young adults: a cohort study to illustrate what events might be mistaken for adverse reactions. *Pediatr Infect Dis J* 2007; 26: 979–84. doi:10.1097/INF.0b013e318149dfea

8 Heley S, Brotherton J. I've had the HPV vaccine: why is my Pap test abnormal? *Aust Fam Physician* 2009; 38: 977–9.

9 WHO. Summary of HPV surveillance and monitoring meeting, 6–7 May 2009, Geneva, Switzerland. Version: 20 July 2009. Available online at: http://www.who.int/nuvi/hpv/HPV_Monitoring_Meeting_Report_May_2009.pdf [verified June 2010].

10 Wilkinson DE, Baylis SA, Padley D, Heath AB, Ferguson M, *et al*. Establishment of the 1st World Health Organization international standards for human papillomavirus type 16 DNA and type 18 DNA. *Int J Cancer* 2010; 126: 2969–83.

11 Canfell K. Models of cervical screening in the era of HPV vaccination. *Sex Health* 2010; 7: 359–67. doi:10.1071/SH10016

12 Regan DG, Philp DP, Waters EK. Unresolved questions concerning human papillomavirus infection and transmission: a modelling perspective. *Sex Health* 2010; 7: 368–75. doi:10.1071/SH10006

13 Gertig D, Brotherton J, Saville M. Measuring human papillomavirus (HPV) vaccination coverage and the role of the National HPV Vaccination Program Register, Australia. *Sex Health* 2010; in press. doi:10.1071/SH10001

14 National Health and Medical Research Council. The Australian Immunisation Handbook, 9th Edition. Canberra: Australian Government; 2008.

15 Duclos P. A global perspective on vaccine safety. *Vaccine* 2004; 22: 2059–63. doi:10.1016/j.vaccine.2004.01.010

16 Lawrence G. National Vaccine Safety Workshop: summary and draft recommendations. *Commun Dis Intell* 2006; 30: 378–80.

17 Gold M, Buttery J, McIntyre P. Human papillomavirus vaccine safety in Australia: experience to date and issues for surveillance. *Sex Health* 2010; 7: 320–4. doi:10.1071/SH09153

18 Lawrence G, Gold MS, Hill R, Deeks S, Glasswell A, McIntyre PB. Annual report: surveillance of adverse events following immunisation in Australia, 2007. *Commun Dis Intell* 2008; 32: 371–87.

19 Stevens M, Tabrizi SN, Brotherton J, Condon J, McIntyre P, Smith D, *et al.* HPV genotype prevalence among Australian women prior to vaccine implementation. Poster 26.026. 25th International Papillomavirus Conference, May 8–14, 2009. Malmo, Sweden.

20 Stevens M, Tabrizi S, Quinn M, Garland S. Human papillomavirus genotype prevalence in cervical biopsies from women diagnosed with cervical intraepithelial neoplasia or cervical cancer in Melbourne, Australia. *Int J Cancer* 2006; 16: 1017–24. doi:10.1111/j.1525-1438.2006.00453.x

21 Brestavoc B, Harnett G, Smith D, Frost F, Shellam G. Human papillomavirus genotypes and their association with cervical neoplasia in a cohort of Western Australian women. *J Med Virol* 2005; 76: 106–10. doi:10.1002/jmv.20330

22 Castle PE, Schiffman M, Wheeler CM, Solomon D. Evidence for frequent regression of cervical intraepithelial neoplasia-grade 2. *Obstet Gynecol Surv* 2009; 64: 306–8. doi:10.1097/01.ogx.0000347334.07172.51

23 Mitchell H, Hocking J. Influences on the risk of recurrent high grade cervical abnormality. *Int J Gynecol Cancer* 2002; 12: 728–34. doi:10.1046/j.1525-1438.2002.01153.x

24 Brotherton JML. How much cervical cancer in Australia is vaccine preventable? A meta-analysis. *Vaccine* 2008; 26: 250–6. doi:10.1016/j.vaccine.2007.10.057

25 Clifford G, Smith J, Aguado T, Franceschi S. Comparison of HPV type distribution in high-grade cervical lesions and cervical cancer: a meta-analysis. *Br J Cancer* 2003; 89: 101–5. doi:10.1038/sj.bjc.6601024

26 Clifford G, Rana R, Franceschi S, Smith J, Gough G, Pimenta J. Human papillomavirus genotype distribution in low-grade cervical lesions: comparison by geographic region and with cervical cancer. *Cancer Epidemiol Biomarkers Prev* 2005; 14: 1157–64. doi:10.1158/1055-9965.EPI-04-0812

27 Alam N, Banks C, Chen W, Baker D, Kwaan G, Bishop J. Cervical cancer screening in New South Wales: annual statistical report 2005. Sydney: Cancer Institute NSW; 2008.

28 Budd A, Sturrock A. Cytology and cervical cancer surveillance in an era of human papillomavirus vaccination. *Sex Health* 2010; 7: 328–34. doi:10.1071/SH09133

29 Garland SM, Steben M, Sings HL, James M, Lu S, Railkar R, *et al*. Natural history of genital warts: analysis of the placebo arm of 2 randomized phase III trials of a quadrivalent HPV (types 6, 11, 16, 18) vaccine. *J Infect Dis* 2009; 119: 1–10.

30 Garland S, Hernandez-Avila M, Wheeler CM, Perez G, Harper DM, Leodolter S, *et al*. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N Engl J Med* 2007; 356: 1928–43. doi:10.1056/NEJMoa061760

31 Fairley CK, Hocking JS, Gurrin LC, Chen MY, Donovan B, Bradshaw CS. Rapid decline in presentations of genital warts after the implementation of a national quadrivalent human papillomavirus vaccination programme for young women. *Sex Transm Infect* 2009; 85: 499–502. doi:10.1136/sti.2009.037788

32 Derkay CS, Wiatrak B. Recurrent respiratory papillomatosis: a review. *Laryngoscope* 2008; 118: 1236–47. doi:10.1097/MLG.0b013e31816a7135

33 Rosenthal DA, Dyson S, Pitts M, Garland SM. Challenges to accepting a human papillomavirus (HPV) vaccine: a qualitative study of Australian women. *Women's Health* 2007; 45: 59–73. doi:10.1300/J013v45n02_04

34 Pitts MK, Dyson SJ, Rosenthal DA, Garland SM. Knowledge and awareness of human papillomavirus (HPV): attitudes towards HPV vaccination among a representative sample of women in Victoria, Australia. *Sex Health* 2007; 4: 177–80. doi:10.1071/SH07023

35 Brewer NT, Fazekas KI. Predictors of HPV vaccine acceptability: a theory-informed, systematic review. *Prev Med* 2007; 45: 107–14. doi:10.1016/j.ypmed.2007.05.013

36 Cooper Robbins SC, Bernard D, McCaffery K, Brotherton J, Garland S, Skinner SR. "Is cancer contagious?" Australian adolescent girls and their parents: making the most of limited information about HPV and HPV vaccination. *Vaccine* 2010; 28: 3398–408. doi:10.1016/j.vaccine. 2010.02.078

37 Donovan B, Fairley C. What can surveillance of genital warts tell us? *Sex Health* 2010; 7: 325–7. doi:10.1071/SH09145

38 Novakovic D, Cheng ATL, Cope DH, Brotherton JML. Estimating the prevalence of and treatment patterns for juvenile onset recurrent respiratory papillomatosis in Australia pre-vaccination: a pilot study. *Sex Health* 2010; 7: 253–61. doi:10.1071/SH09142

Manuscript received 2 December 2009, accepted 13 April 2010