UPDATE/ NEW SUB-SECTION:

1.3.3 Organised immunisation of young people

In 2007, human papillomavirus (HPV) vaccination was introduced for all young Australian women aged between the ages of 12 and 26 years. Australia was the first country in the world to initiate and fully fund a national vaccination program using a quadrivalent HPV vaccine.[1,2]

> *"Australian women [were] the first cohort of young women in the world to be vaccinated against a range of human papillomavirus (HPV) related diseases, including cervical cancer".*[2:96]

Human papillomavirus (HPV) is a causative agent for cervical cancer and its pre-malignant precursor stages, and papillomaviruses were the first infectious agents to be unequivocally associated with tumour formation.[3,4] Chronic infection with HPV was the cause of around 70-80% of all cervical cancers; and specific types of HPV also produced other HPV-related diseases.[3,5,6:113,7] HPV infection itself was generally asymptomatic and usually not recognised until patients were diagnosed with cervical dysplasia, cancer or genital warts.[2] Although HPV infection was common, with around 70% of both males and females showing evidence of HPV infection within five years of becoming sexually active, in the majority of cases, infection resolved within 36 months. [2,8]

After a period of declining incidence from 1982-2000, cervical cancer case rates in Australia plateaued, mainly due to Australia's cervical screening program. From 2002 to 2010 (the last year for which the Australian Institute of Health and Welfare held national data in 2014), about seven in every 100,000 Australian women were newly diagnosed annually. Available data also indicated that newly diagnosed cases in Aboriginal and Torres Strait Islander women were almost three times as high (data from 2004-2008 for NSW, Qld, WA and the NT only).[6]

Although cervical cancer was known for many years to be associated with sexual transmission, it was not until the 1990s that medical research established the plurality of HPV types and the role of specific types in cervical cancer (with at least 200 known types of HPV in 2010[4]).[3] From early studies, it was clear that two types, known as HPV-16 and HPV-18, were strongly associated with cervical cancer. Of the forty types of HPV that could infect the mucosal epithelium, four high-risk (cancer-causing) types were determined to be preventable using prophylactic (or 'disease-preventing') vaccination. Two of these types (HPV-16 and -18) were determined to cause at least 70% of cervical cancers, a proportion of other genital cancers, and a portion of head and neck cancers, while the low-risk (non- cancer causing) types HPV-6 and -11 caused 90% of genital warts and the disease, recurrent respiratory papillomatosis.[9] The vaccines that were developed targeted these four HPV types, and the production and testing of quadrivalent and bivalent HPV vaccines (targeting HPV-16 and -18 only) were undertaken commercially during the 1990s.[4] Clinical trials demonstrated that the HPV vaccines were safe and effective in preventing infection and disease in 'naïve' females who were not already infected.[4] The quadrivalent HPV vaccine was licensed and approved for use in Australia in 2006 (and for the European and US markets); and from April 2007, HPV vaccination was introduced nationally for all young Australian women aged between 12 and 26 years. Future vaccines could contain more HPV types.[4]

> "Vaccines against the high risk HPV types 16 and 18 represent the first preventive vaccines directly developed to protect against a major human cancer (cervical carcinoma)."
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> **— zur Hausen H. Papillomaviruses in the causation of human cancers - a brief historical account. *Virology* 2009; 384: p. 260.[3]**

Public health practices

Australia's HPV vaccination program commenced in April 2007, using the quadrivalent HPV vaccine, for girls who were 12 to 13 years of age, through school-based programs delivered by the states and territories on an ongoing basis. Two-year catch-up programs were offered to girls aged 14 to 17 years through school-based programs, and to young women (18 to 26 years of age) in community-based settings, such as GP clinics. From 2013, the HPV vaccine was included in the National Immunisation

Program (NIP) and routinely provided for all girls and boys aged 12 to 13 years through school-based programs. Catch-up vaccination was available for males aged 14 to 15 years in 2013 and 2014.[10] Vaccination was delivered as a three-dose course, and immunisation was monitored and evaluated through the *National HPV Vaccination Program Register*.[10] Administration of all three doses was important for optimal protection from the vaccine, so compliance had to be encouraged and monitored.[2]

Vaccination was not an alternative to regular Pap tests, and regular testing continued to be recommended as per the national cervical screening guidelines: together these two approaches provided the best protection.

The *National HPV Vaccination Program Register,* which commenced operation in 2008 (at the Victorian Cytology Service Inc.), was conceived as fundamental to support the National HPV Vaccination Program.[11] As cervical cancer took a relatively lengthy time to develop (up to decades), it would not be known whether, or to what extent the vaccine had been successful in preventing cervical cancer for some years, although the initial signs were positive. A decrease in the incidence of high-grade cervical abnormalities was first recorded in girls aged less than 18 years within three years of the implementation of the HPV vaccination program in schools in Victoria.[12]

> "The HPV vaccine is a relatively new, expensive vaccine aimed at pre-adolescent girls, groups that are infrequently targeted by vaccination programs, and protects against disease outcomes that would occur many years or decades in the future. Therefore there is great interest and importance placed on monitoring vaccine coverage and effectiveness. Systems should ideally be designed and put in place at the commencement of the vaccination program, as collection of data retrospectively leads to potential incomplete and inaccurate information."
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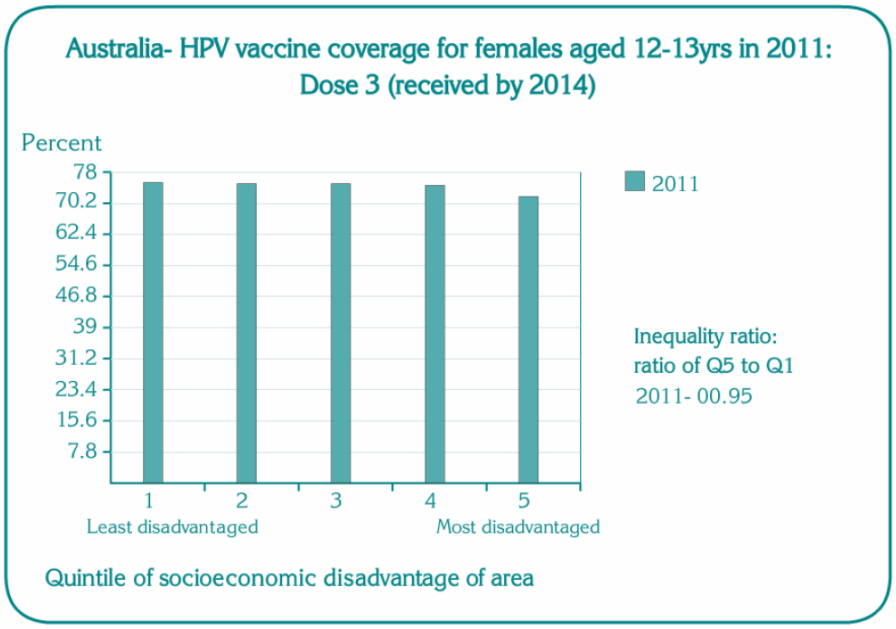
> **— Gertig DM, Brotherton JM, Saville M. Measuring human papillomavirus (HPV) vaccination coverage and the role of the National HPV Vaccination Program Register, Australia.** ***Sexual Health*** **2011; 8(2): 176. [11]**

These results were confirmed over the five years following implementation of the HPV vaccination program in schools (2007-2011), with demonstrated reduced cervical abnormalities for vaccinated women.[13] As expected, the greatest vaccine effectiveness was seen in the youngest women.[13] In 2010-2011, an annual average of 3,794 women under 25 years of age had high-grade cervical abnormalities detected, and this was about 700 a year fewer than in 2004-2006 before the HPV vaccine was implemented.[6] The effect of the HPV vaccine was expected to increase over time as women who were vaccinated as girls (at 12-13 years) reached the ages where cancer incidence was more common. Reductions in genital warts – in both young women and young men – and in other (non-cervical) HPV-related cancers – were also expected. [1,6,14,15-17]

The HPV Register supported the National HPV Vaccination Program by monitoring and evaluating the Program, and data held on the Register had the potential to be linked with state and territory cervical cytology registers and Cancer Registries. Linking cervical cytology outcomes to vaccination status would allow direct measures of vaccine effectiveness to be made, comparing rates of cervical abnormality diagnoses between vaccinated and unvaccinated women.[18] The Immunise Australia Program reported immunisation coverage rates and cohort-level catch-up program penetration, with Australia's HPV vaccination coverage reported in the peer-reviewed literature.[11,19-22] There was also an established procedure for reporting adverse events (via the Therapeutic Goods Authority adverse event reporting system).[10] A total of 1,394 suspected adverse events following immunisation (AEFI) were reported to this passive surveillance system as at August 2009, compared with more than 5.8 million doses that were distributed.[23]

Data from the Register was used to evaluate and assess coverage rates as well as finer grade analyses, such as coverage rates by quintiles of socioeconomic disadvantage of area prepared by PHIDU. *Figure 1.3.3.a* shows the differences across these quintiles for three dose vaccine coverage in females aged 12 to 13 years in 2011, with the lowest rates apparent in those living in the most disadvantaged areas.[24]

Figure 1.3.3.a: HPV vaccine coverage for females aged 12-13 years in mid-2011, who received Dose 3 of the vaccine by 2014 – by Quintiles of Socioeconomic Disadvantage of Area, for Australia



Notes:
1. The data presented are for females who were aged 12 to 13 years as at 30 June 2011, and who received three doses of the HPV vaccination by 31 October 2014. Females receiving all three doses represent those fully vaccinated.
2. Inequality graphs show variations by socioeconomic status (SES), based on the ABS Index of Relative Socioeconomic Disadvantage (IRSD). Data are presented in five groupings of areas ('quintiles' or, as labelled within the graph interface, 'Quintile of Socioeconomic Disadvantage of Area'), each representing approximately one fifth (20%) of the population. The quintiles range from the 20% of the population living in the highest SES areas (least disadvantaged) to the 20% living in the lowest SES areas (most disadvantaged). The height of the bar for each quintile indicates the rate or per cent for the population usually resident in that quintile. The ratio of the rate in the most disadvantaged areas (Quintile 5) to that in the least disadvantaged areas (Quintile 1) is shown on the right hand side of the graph: it is labelled the 'Inequality ratio'.

Source: Compiled by PHIDU using data from the National HPV Vaccination Program Register (NHVPR), December 2014; and the ABS Census Usual Resident Population (URP) 2011.[24]

Factors critical to success

The HPV vaccination program had a measurable impact on young people's health, as well as the general population. It addressed a significant health problem, was ambitious in scope, functioned nationally as a universal program, used vaccines judged to be cost-effective at the scale required to provide adequate coverage, and was cost-effective. To remain successful, herd immunity across the young adult population needed to be maintained.

The effectiveness of the HPV vaccination program was established early as decreases in high-grade cervical abnormalities were seen within the first three years following its inception, as well as a rapid decline in genital warts.[1,12,25,26]

The program was aimed at those who were most at risk, with young women and girls of ages 12 to 26 years targeted through a number of settings, including schools and catch-up programs in GP clinics. Boys and young men were similarly targeted in schools and catch-up programs in community settings when the program was extended in 2013. These program designs illustrated the use of appropriate settings such as schools and GP practices that best suited delivery for the target ages. Despite the known difficulties with vaccination of adolescents and young people, the program achieved coverage that exceeded similar programs addressing the same target groups (e.g., measles catch-up programs).[21]

The HPV Immunisation Program in Australia satisfied all the conditions identified by Shefer and colleagues as necessary for the successful integration of a new vaccine into an established national vaccination program. These included:

- national recommendations to add the vaccine to the program;
- education of, and acceptance by the public and medical community;
- appropriate infrastructure for vaccine delivery and support;
- financing of the vaccine and the program; and
- political will.[28]

> "HPV vaccination has been introduced for less than 7 years and as such, it is difficult to quantitate the effect it will have on the incidence of cervical, vulvar/vaginal, penile, anal and other cancers. There is very strong, some say conclusive data, that HPV is the root cause of over 99% of cervical cancers. HPV vaccination has been clearly demonstrated to reduce the incidence of the pre-cancerous markers of cervical cancer, in trials involving over 44,000 women, and the resulting effects on cervical cancer incidence will become clearer over time with the aid of post-marketing surveillance."
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> **—Hawkes D, Lea C, Berryman M. Answering human papillomavirus vaccine concerns; a matter of science and time.** ***Infectious Agents and Cancer*** **2013; 8(1): 22.[27]**

Cost-effectiveness

In Australia, the initial rationale for the HPV vaccination program was based on the cost-effectiveness estimates for the implementation of a vaccination program for 12- to 26-year old females.[2,29] A cervical cancer lifetime risk reduction of 48% was calculated by comparison with the National Cervical Screening Program, based on a set of assumptions including 100% vaccine effectiveness, lifetime duration of efficacy, and an 80% coverage rate for immunisation.[2,29] Kulasingam and colleagues concluded that "adding an HPV vaccine to Australia's current screening regimen is a potentially cost-effective way to reduce cervical cancer and the clinical interventions that are currently associated with its prevention via screening alone."[29] In 2007, Regan and colleagues concluded that, for Australia, mass vaccination with a highly effective vaccine against HPV-16 had the potential to reduce the incidence and prevalence of infection substantially; and catch-up vaccination could substantially reduce the delay before the benefits of vaccination were observed.[30] (Note that they also thought that a booster vaccination might be required in women (25 years and older) to prevent an increase in incidence of infection, and that facility was included in the Register.[11,30])

Smith and colleagues predicted that the impact of the HPV vaccination program would substantially and rapidly reduce the age-standardised incidence of HPV-16 infections by 56% by 2010 (range 48-61%), and by 92% by 2050 (range 76-95%), based on coverage estimates of 86% (range 67-90%) for 12- to 13-year old girls in 2007/2008, with lower coverage rates likely in older females.[31] Although vaccinating only females was expected to confer benefit also on heterosexual males (for instance, one study estimated that a 68% reduction in male HPV-16 infections by 2050 would lead to an projected long-term reduction of 14% in rates of cancers of the head, neck and anogenital areas[32]), it would not address HPV-related conditions in homosexual males.

The incidence of other HPV-related cancers (e.g., oropharyngeal cancers[16]), which were increasing in Australia, formed part of the evidence for the case to extend the HPV vaccination program to boys and young men.[15-17] For example, determination of the HPV status of 302 oropharyngeal cancers diagnosed between 1987 and 2006 showed that the overall HPV-positivity rate was 36% (with 94% being types HPV-16 and -18), and HPV-related cancer increased from 19%(1987-1990) to 47%(2001-2005).[16]

Estimating the effectiveness and cost-effectiveness of HPV vaccination remained a complex task, with a number of important limitations in the economic evaluations performed to date. These included minimal exploration of different screening options as the comparator, lack of adjustment of the comparator to the margin, and the use of a static model, hence ignoring the infectious nature of HPV. These and other complexities were reviewed by Beutels and Jit, who considered that, despite the difficulties for developed countries, vaccinating cohorts of girls before their first sexual experience, with additional catch-up vaccinations (both covering girls aged 9 to 18 years), were likely to be cost effective, although they noted that the less well-organised the initial screening program, the more gain was to be had from a well-organised catch-up vaccination program.[33] Like others, they did not consider it likely to be cost-effective in boys and young males.[33,34]

The impact on genital warts (90% of which were estimated to be prevented by the quadrivalent vaccine used in Australia) was also ignored in many cost-effectiveness analyses.[33] However, as genital warts were responsible for a large healthcare burden, this was potentially one of the earliest success stories. In 2010, Pirotta and colleagues concluded that the healthcare resources dedicated to managing genital warts were considerable, and included hospitals, specialists and GP services at a projected cost of more than $14 million annually (estimated treatment cost per case: $386 for women and $251 for men).[35] Although the annual incidence of genital warts per 1,000 Australians was estimated at 2.19 cases, the peak in young women (20-24 years) was 8.61 cases per 1,000 and in young men (25-29 years), 7.40 cases per 1,000.[35]

The quadrivalent human papillomavirus vaccine had the potential to reduce this burden significantly, and there were early indications that this had occurred. For instance, a Melbourne Sexual Health Centre reported in 2015, just seven years after the national HPV vaccination programme began, that genital warts were now rare in young Australian women and heterosexual men (aged less than 21 years) (although they remained common in men who had sex with men).[25,26] A similar effect was seen earlier (in 2009) in national sentinel surveillance data of patients attending eight sexual health services in Australia, and it was posited that heterosexual men were benefitting from the high HPV immunisation coverage of young women (reportedly, by 65%).[1]

Future challenges

Challenges for the future included the development of vaccines that contained additional HPV types, especially the high risk of cancer-causing types. The next generations of HPV vaccines were already under development[36]; and costs to the public health system needed to be realistic in terms of the likely gains.

At issue for the future was a better understanding of the complexities behind the causes of cervical cancer. Although HPV infection was necessary, it was not always sufficient, with environmental and behavioural factors (as well as the possibility of genetics[37]) playing a part in the incidence of HPV-related lesions that then progressed to cervical cancer. These other factors also needed to be tackled, especially in those sub-populations that were over-represented in cervical cancer cases (and often under-represented in cervical screening programs).[37,38]

Sustaining and improving HPV vaccination coverage in young Australian women and men to build up and ensure herd immunity, while maintaining cervical cancer screening participation and reviewing cervical cancer screening methods, were ongoing challenges.[39] There was a risk that vaccinated women might not present for screening as frequently as unvaccinated women. Evidence suggested that this had already occurred, with screening participation rates for vaccinated and unvaccinated Victorian women during the period 2010-2011, revealing lower cervical screening for 20-29 year old vaccinated women when compared with unvaccinated women of the same ages.[40] Education on the continuing need for cervical screening, as well as the implementation of a range of activities to increase participation in cervical screening by vaccinated women were required.[40,41]

Implementation of HPV vaccination demonstrated the need for cervical screening and immunisation programs to work together. Assessing the coverage and role of the HPV Register, Gertig and colleagues proposed a combined register, a "cervical cancer prevention register" to support both HPV vaccination and cervical screening programs and which could incorporate vaccination status, cytology, histology and (anticipated future) HPV DNA test results. Such developments were viewed as "maximising the protection against cervical cancer for women of all ages".[11:176-177]

The remaining challenge lay in revising the models that were used to quantify the benefits and costs of HPV vaccination programs so that they reflected the actual gains more accurately. This could only be achieved over time as additional data became available, assumptions were proven (one way or the other) and further knowledge evolved.

Table: Historic highlights of the organised immunisation of young people

1970s-	Medical research established the plurality of human papillomavirus (HPV) types and the role of specific types in cervical cancer.[3]
1980s	Increasing acceptance of HPVs as the likely causative agents for some anogenital cancers.[4]
late 1990s	Production and testing of bivalent and quadrivalent HPV vaccines undertaken commercially.[4]
2006	Quadrivalent HPV vaccine licensed and approved for use in the population (also approved for the European and US markets).
2007	A fully funded national vaccination program using quadrivalent HPV vaccine approved for Australian females aged between 12 and 26 years (the first country to do so). Enabling legislation authorised national collection of data on administered HPV vaccine doses from state and territory governments and health professionals.
2008	The *National Human Papillomavirus (HPV) Vaccination Program Register* (HPV Register) commenced. Nobel Prize in Physiology/Medicine awarded to Professor Harald zur Hausen for his team's discovery of specific types of HPV that caused cervical cancer.
2011	The Pharmaceutical Benefits Advisory Committee accepted the quadrivalent HPV vaccine for boys and young males for listing on the National Immunisation Program (after rejecting the first-time application on the basis of an unacceptably high and uncertain cost-effectiveness analysis).[42]
2013	The National Immunisation Program (NIP) extended to adolescent males in another world-first – providing fully funded HPV vaccination to females and males aged 12-13 years, delivered through schools, with a short-term catch-up program offered in 2013 and 2014 to males aged 14-15 years.[10]
2015	Genital warts reported as rare in young Australian women and heterosexual men aged 21 years and less.

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