Review Article

The Australian Experience With the Human Papillomavirus Vaccine

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ABSTRACT

Objective: The goal of this study was to review the current human papillomavirus (HPV) vaccine program and its outcomes to date in Australia.

Methods: This was a review of the published data relating to the introduction and subsequent measurable outcomes of the quadrivalent vaccine, which became part of the Australian national HPV immunization program in 2007. Australia commenced an ongoing, schoolbased, government-funded, HPV vaccination program using the quadrivalent vaccine from April 2007 for adolescent female subjects aged 12 to 13 years, together with a catch-up program for female subjects 13 to 26 years of age from July 2007 to December 31, 2009.

Results: The Australian community (lay and clinical) have embraced the program, resulting in high coverage with >70% for 3 doses in the 12- to 13-year-old ongoing target population. Vaccine effectiveness (outcomes of vaccination in a real-world setting) is already being seen. This effectiveness has been noted in significant reductions in HPV vaccine–related infections in vaccine eligible age female subjects (77% fall in prevalence), rapid reduction of >90% in genital warts (first marker of disease reduction, as well as herd immunity), and reduction in high-grade cervical lesions in this age group. These remarkable changes so soon after implementation of the vaccine in the country occurred faster, and to a greater extent, than anyone could have predicted.

Conclusions: These findings from Australia should encourage other countries to follow suit, with the ultimate aim of translating treatment into reductions in HPV-related neoplasia globally. The greatest success from such an approach will only be realized when prophylactic vaccines are rolled out effectively, with high coverage and at affordable costs, to those areas of the world with the highest burden of disease. To achieve this outcome requires government endorsement and commitment; education of the community at large; realization of the safety, efficacy, and immunogenicity of the available prophylactic vaccines in reducing HPV-related infections and disease, especially neoplasia; and governments procuring vaccines at affordable prices through the various options now available (eg, support from the GAVI Alliance to eligible countries, tiered pricing, negotiation with pharmaceutical manufacturers). We have the tools to reach this goal, and it is time these tools were implemented. (*Clin Ther*. 2014;36:17–23)

Key word: Human Papillomavirus, Quadrivalent vaccine, cervical cancer, genital warts, safety, cervical screening, vaccination, vaccine effectiveness.

INTRODUCTION

Australia is a large country with a relatively small population (~22 million people), most of whom are

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concentrated around the coastal regions.[1] Australia has led the way in preventing cervical cancer, both from a primary as well as a secondary point of view. With respect to secondary screening, Australia moved from an opportunistic to an organized cervical cytology approach in 1991, in a program called the National Cervical Screening Program (NCSP).[2] The NCSP is a comprehensive system that promotes routine screening with conventional cytology, every 2 years for women 18 years of age or 2 years after sexual debut (whichever is later) to the age of 69 years. This program has seen a large drop in the incidence of cervical cancer of more than one half, from 13.2 per 100,000 in the early 1980s to 6.9 per 100,000 most recently. Moreover, the mortality for this time period has dropped from 4 to 1.9 per 100,000. Accordingly, as a result of the NCSP program, cervical cancer is now the 13th most common cancer in women in Australia, compared with other countries, particularly those that are resource-poor and where cervical cancer can be the first or second most common cancer in women.[3] The NCSP is currently being reviewed (known as the National Cervical Screening Program Renewal) in light of the success of the cervical cancer vaccine program, and largely as the vaccine reduces vaccine human papillomavirus (HPV) type–related cervical lesions, the positive predictive value of cytology will decline.[4] We await the outcome of these deliberations, although it is predicted that Australia will follow other recommendations worldwide of commencing screening later, adopting wider screening intervals, and possibly using more sensitive assays. In the meantime, however, it is noteworthy that with a screening program of every 2 years (with a resultant 70%[5] 3 yearly uptake rate in the target population) from 18 years of age overlaps the vaccination age and has allowed the successful measure of the impact of the vaccine in the decline of vaccine-related HPV type high-grade disease or cervical intraepithelial neoplasia (CIN) in the catch-up population.[6,7]

The goal of the present study was to review the current HPV vaccine program and its outcomes to date in Australia.

METHODS

Review of published data and unpublished data presented at scientific forums relating to the introduction and subsequent measurable outcomes of the quadrivalent vaccine, which became part of the Australian national immunization program in 2007.

RESULTS

HPV Vaccination: Primary Prevention Program for Cervical Cancer

In 2007, after the successful Phase III clinical trials of the quadrivalent HPV vaccine,[8,9]* Australia adopted a primary approach to cervical cancer prevention by introducing, through the National Immunisation Program (NIP), the HPV vaccine, otherwise known as the cervical cancer vaccine.[10] This is an ongoing program in which the quadrivalent vaccine is offered free of charge to girls aged 12 to 13 years, primarily through schools. In addition, at the outset of this program, there was a 2-year catch-up initiative, which commenced in July 2007 and ended in December 2009, in which the vaccine was offered to female subjects aged 13 to 26 years via community-based programs, general practices, and schools. The NIP is the process whereby all recommended childhood vaccines are funded by the national government. For vaccines targeted to the adolescent age group, the majority are provided by school-based immunization teams and coordinated through local government or regional health authorities. It is noteworthy that school-based immunization nurses are certified to perform vaccines, including proficiency in measures to adopt for vaccine-related adverse responses at the time of injection. In general, there is good acceptance of vaccination in Australia, with coverage of recommended childhood vaccines $>90\%$ for 2-year-olds and $\sim 80\%$ for 5-year-olds.[11]

HPV Vaccination National Immunization Program Processes

Australia's childhood vaccination program is supported by a national childhood immunization register that issues reminders to parents and general practitioners of recommended vaccines, provides financial incentives for parents and general practitioners to complete vaccinations, and offers legislation that requires parents to provide a record of their child's immunization status at primary school entry. Vaccination is not compulsory in Australia, however. An immunization record is required in primary school so that unvaccinated children can be excluded from school in the event of a vaccine-preventable disease outbreak. In general, consent forms and information brochures are taken home to parents/guardians by

*Trademark: Gardasil® (Merck & Co, Inc, Whitehouse Station, New Jersey).

students, and the signed consent forms are then returned to the school and collected by the teacher. On the vaccination day, students with a parental signature indicating consent will receive the vaccine to which this applies. For HPV, the medical profession and the lay public at large have effectively endorsed this program, resulting in high coverage of 3 doses at 73% in the 12- to 13-year-old age group.[12]

Monitoring the HPV Vaccine Program

Because the current childhood vaccine registers in place could not accommodate adolescent HPV vaccines, monitoring of vaccine coverage was assisted by establishment of a National Human Papillomavirus Vaccination Program Register (NHVPR).[12] The NHVPR was created by legislation with the goal of collecting data about HPV vaccines administered to female subjects across all settings and to assist with monitoring the program's impact through eventual data linkage to Papanicolaou cytology test results and cervical cancer registers. The legislation allows for vaccination information to be forwarded to the NHVPR, unless the woman vaccinated (or parent in the case of vaccinated school-girls) objects (an opt-off process). Although this notification system is compulsory for those HPV vaccines delivered through the states' school programs (apart from those who have opted-off), this process is not compulsory for general practitioners, although it is highly encouraged. Consequently, vaccinations administered to those aged >18 years in the catch-up program are likely undernotified. In recently published data extracted from the NHVPR as of July 2012 (table), it can be seen that moderately high coverage was achieved across the various age-stratified school-based cohorts (3-dose coverage of 72%/72%/70% for 12- to 13-year-olds, 14- to 15-year-olds, and 16- to 17-year-olds, respectively).[13] Coverage of the first dose was at least 10% higher (at 83%/82%/82%). A trend toward lower coverage in older school-age cohorts is also consistent with other vaccines recommended in this age group in Australia. In those young women beyond school-age, undernotification to the register may have reduced estimates of 1-dose coverage (76% and 55%) and 3-dose coverage (62% and 32% for 18- to 19-year-olds and 20- to 26-year-olds, respectively). Independent estimates of coverage in young women in clinical and general practice populations, and the coverage estimates from those jurisdictions with central notification of vaccination data from general practices, suggest higher coverage (by at least ~10%–20%)[14–17] (unpublished observations, S.M.G.).

Adverse Event Surveillance

Adverse events after immunization are monitored through passive surveillance. Within each state and territory, there are various levels of enhanced safety monitoring. In Victoria, for example, the state government established a new service called SAEFVIC (Surveillance of Adverse Events Following Vaccination in the Community) in April 2007.[18] This surveillance was pertinent in following up and defining rates of potential adverse events from the HPV vaccine program when it first commenced.[19] Having a risk management strategy is important to effectively and quickly deal with episodes of adversity and to maintain general population and medical confidence in such newly adopted vaccine

Table. Human papillomavirus (HPV) vaccination coverage by dose number and age (as of mid-2009) as notified to the National Human Papillomavirus Vaccination Program Register (women vaccinated between April 1, 2007, and June 30, 2012).

Place of Vaccination	School Program	School Catch-up	School Catch-up	GP/Community	GP/Community
Age, y (at mid-2007)	12–13	14–15	16–17	18–19	20–26
Population (at mid-2007)	273,825	281,072	285,487	300,475	1,102,965
Total no. of doses notified	639,402	652,642	654,209	626,121	1,450,558
Coverage rate as of March 21, 2011; dose 1	83%	82%	82%	76%	55%
Coverage rate as of March 21, 2011; dose 2	79%	78%	77%	70%	45%
Coverage rate as of March 21, 2011; dose 3	72%	72%	70%	62%	32%

GP = general practice.
From the National Human Pamillomavirus Vaccination Program Register, used by permission of the Australian Government.

programs. The recently published population-based cohort study from Denmark provides strong evidence against autoimmune and neurologic, as well as venous thromboembolic, events.[20]

Genital Wart Surveillance: The First Indicator of Disease Reduction From Impact of Vaccination

In monitoring the impact of the HPV vaccine program, the primary outcome we aim for is reduction in HPV-related neoplasia. However, this goal will take decades given the time course from infection with oncogenic HPVs and subsequent mutagenic events resulting in precancers (high-grade dysplasias) to cancer. Furthermore, it would have been unethical to have cancer as a primary outcome in clinical trials. Considering various surrogates for the HPV-related genotypes and their relative incubation periods, it is not surprising that genital warts were the first indicators of disease affected by good coverage of the vaccine in public health programs. We are reminded that in the analysis of the placebo arm of the Phase III clinical trials of the quadrivalent vaccine, that young women with <5 sexual partners, median age of 20 years, and median lifetime number of sex partners of 2 (followed up over 4 years) had an incidence rate of genital warts related to HPV types 6 and 11 of 0.87 case per 100 years at risk. Moreover, HPV types 6 and 11 were detected in the majority of genital warts biopsied (95% of those HPV DNA positive), with risk factors for these genital warts being infection at baseline, acquisition of new sexual partners, and a higher number of sexual partners.[21] It was shown in Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I[8] and FUTURE II[9] that the efficacy for genital warts with HPV types 6/11/16/18 was 99% and remained the same when both lots of data were combined.[22]

Genital warts are not a notifiable disease in Australia. In a retrospective study performed in major sexual health clinics in Australia and before the introduction of the school-based, government-funded vaccine, the burden of disease from genital warts was reported as high. There was an estimated annual incidence of 2.19 cases per 1000 Australians (9% CI, 1.88–2, 2.49) with peak incidence in women aged 20 to 24 years at 8.61 cases per 1000 and in men aged 25 to 29 years at 7.4 cases per 1000.[23,24] Hence, genital warts contribute to a large burden of disease in sexual health settings. Moreover, these findings translate into a high financial burden, at an estimated annual cost of management of genital warts of more than A$14,000,000; the estimated cost per treated case is A$251 for men and A$386 for women.[24] In addition, in a study performed in a sexual health and gynecologic practice, there was a significant psychosocial burden for women diagnosed with anogenital warts, in contrast to those with normal cytology results and equivalent to those requiring ablative treatment for high-grade dysplasia.[25]

Very early after the introduction of the vaccine program, Australia's largest sexual health clinic (Melbourne Sexual Health Centre) reported a significant reduction in genital warts of 50% to December 2008; this observation was made regardless of vaccine status of young people attending the clinic.[26] This finding was in the context of no decline in prevalence of other sexually transmitted diseases or infections. It was also noted that there was a reduction in genital wart diagnoses in heterosexual (but not homosexual) men, consistent with reduced heterosexual transmission of HPV as a result of female vaccination. Read et al[27] further updated these data 2 years later (4 years after the vaccine program commenced) and found a 90% drop in genital warts in this clinic in this vaccine-eligible age to June 2011. In a more comprehensive sentinel surveillance network that monitored the effect of the vaccine on cases of genital warts seen at major sexual health services across Australia, it was shown that the changes were restricted to those young women who were eligible for free vaccine, but these changes were not seen in nonresidents.[28] Furthermore, this group reported a marked reduction in genital warts, not only in the female population of vaccine-eligible age of 59%, but also as an effect of herd immunity, a significant drop of 39% in young heterosexual males (who were not part of the free vaccination schedule, and only a few percentage of the eligible-age group were vaccinated in the private market).[28] In a more recent review of these clinics (ie, at 5 years into the national program), the reduction in the group aged <21 years was reported as 93%, and for those aged 21 to 30 years, it was 73%; there was no significant decline for those >30 years of age. Further decreases were seen in heterosexual males: 82% for those aged <21 years and 51% for those aged 21 to 30 years. No changes were seen for male subjects aged >30 years.[29]

In those requiring inpatient treatment of vulval or vaginal warts, there has been a substantial decrease of

85% in treatment numbers from 2007 to 2011 in the youngest women, a finding likely attributable to the HPV vaccine program. The moderate decline in inpatient treatments for penile warts in men probably reflects herd immunity.[30]

Papanicolaou Cytology Surveillance as the Second Indicator of Disease Reduction From Impact of Vaccination

In an early review of Papanicolaou smear abnormalities recorded in the Victorian Cervical Cytology Registry, a modest but significant decrease in high-grade abnormalities was demonstrated in those women aged <18 years between 2007 and 2009 when the HPV vaccination program was delivered, and compared with the prevaccination period; the primary outcome was histologically confirmed high-grade cervical disease (CIN2+/adenocarcinoma in-situ [AIS]).[6] Although it was not possible, using these ecologic data, to confirm whether this reduction was due to vaccination, just published are results from the data linkage study between the Victorian Cervical Cytology Registry and the NHVPR that created a cohort of screening women who were either vaccinated or unvaccinated. These results demonstrated that such reductions in histologically confirmed high-grade lesions are indeed occurring among vaccinated women.[7] In this study period of April 1, 2007, to December 31, 2011, a total of 24,871 women between 12 and 17 years of age who were vaccinated against HPV had commenced cervical screening. It is noteworthy that 85% of these women were completely vaccinated, whereas the remainder had received 1 or 2 doses of vaccine. Vaccine effectiveness for CIN3+/AIS was 47.5% (95% CI, 22.7–64.4) for women who were completely vaccinated compared with 36.4% (95% CI, 9.8–55.1) for those receiving any dose of vaccine. A cautionary note for those considering reduced doses of vaccine is that for those who received only 1 or 2 doses of vaccine (although the number of outcomes was small), the hazard ratios for CIN3+/AIS were not significantly different from 1.0.[20]

Impact of HPV Vaccination on Screening Participation

In a recent data linkage between the NHVPR and the Victorian Cervical Cytology Registry for women of vaccine eligible age for the period 2010–2011, participation was higher among the unvaccinated than the vaccinated.[7] For those aged 20 to 24 years, vaccinated coverage was 39.6% versus 45.9% for unvaccinated subjects ($P < 0.001$). For those aged 25 to 29 years, vaccinated coverage was 48.4% versus 56.6% for unvaccinated subjects ($P < 0.001$.) However, of those vaccinated women who were screened, 11% had their first-ever Papanicolaou smear during their vaccine course.

Reduction in HPV Genotype Infection After HPV Vaccination

We have also recorded a marked reduction in vaccine-related HPV infections (in the order of 77%) in an interim analysis of young women aged 18 to 24 years (who would have been aged 13–21 years at the time of vaccination) presenting for cervical cytology screening to family planning clinics and of vaccine-eligible age.[31] This has been compared with the prevaccine era of a similar population.[32] Of note was the reduction of vaccine-related HPV prevalence in those not vaccinated but of the same age as those being vaccinated: a herd immunity effect.[31] The full analysis of this study, which was recently presented at EUROGIN in November 2013, showed that unvaccinated women had a higher prevalence of any of HPV type 31/33/35/45 than fully vaccinated women (17.4% vs 7.8%; $P = 0.001$).[33] This finding was evidence of a cross-protective effect against types genetically close to the vaccine types.

HPV Vaccination for Male Subjects

As of February 2013, Australia commenced routine male vaccination of first-year high school male subjects (aged 12–13 years), with a catch-up program extending to end of 2014 for 14- to 15-year-olds and as a gender-neutral approach. This program is being run much the same as, and simultaneous with, the young girl program.[34]

Surveillance for Juvenile-Onset Recurrent Respiratory Papillomatosis as a Marker of HPV Type 6/11 Protection

We know that HPV, especially type 11 and as well as type 6, is the major cause of juvenile-onset recurrent respiratory papillomatosis (JORRP).[35] The national prevalence of disease from 2000 to 2010 was estimated at ~0.8 per 100,000 in children aged <15 years.[36] The Australian Paediatric Surveillance Unit is

a mechanism designed to monitor rare diseases such as JORRP.[37] This monitoring will allow regular contact requests to pediatricians and pediatric ear, nose, and throat surgeons for them to complete monthly report cards on whether they have seen cases of JORRP and an opportunity for sending biopsies of lesions for HPV DNA detection and genotyping. Surveillance commenced October 2011 and will assist us in monitoring recurrent respiratory papillomatosis incidence and disease burden over time in the setting of mothers of infants of vaccine eligible age. We will hopefully see a reduction in disease.

Vaccine Effectiveness Studies

Ultimately, well-conducted vaccine effectiveness studies will give us answers regarding the effect of the vaccine program in a real-world situation. We are embarking on a 2-pronged approach in an effectiveness study, measuring genotype prevalence in vaccine-eligible age girls (including a questionnaire on sexual behavior, cervical cytology, and HPV knowledge) and reviewing CIN3 lesions for HPV attribution and using laser microsection.[38]

CONCLUSIONS

We are at the beginning of a potentially great journey (with high coverage and government, clinician, and lay public endorsement) of a vaccine program that ultimately should result in reduction in HPV-related neoplasia. To achieve this end, we must sustain high coverage of vaccination, with ongoing surveillance using linkages between various registries to measure disease outcomes. Now that a neutral-gender approach has been adopted, there is an even greater opportunity to reduce the pool of infection of those viruses causing the bulk of disease.

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CONFLICTS OF INTEREST

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