HPV Vaccines: An overview

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Human papillomavirus and cervical cancer

Papillomaviruses are a large family of DNA viruses that cause epithelial proliferations or warts. The recognition of the pivotal role of human papillomaviruses (HPV) in the aetiology of cervical cancer led to the development of prophylactic vaccines.[1]

There are over 100 types of HPV and around 30–40 of these are known to infect the genital tract – of these around 15 are known to be oncogenic. In New Zealand, despite an active screening programme, there are still about 200 new diagnoses of cervical cancers per year, and approximately 70 deaths. Māori and Pacific women have disproportionately higher rates of cervical cancer than other women.

HPV is also a significant contributor to other genital tract cancers and is estimated to contribute in up to 85% of anal cancers, 50% of vaginal, vulval and penile cancers, 20% of oropharyngeal cancers and 10% of pharyngo-laryngeal cancers.

Vaccines against HPV

There are currently two vaccines available, both with similar technology targeting HPV 16 and 18 viruses. The key differences are summarised in Table 1.

While the prevalence of HPV types are unknown in the New Zealand population, types 16 and 18 combined are implicated in approximately 70% of cervical cancer internationally and a further six serotypes contribute another 20%.

Gardasil™ is a quadravalent vaccine (four antigens), also containing HPV types 6 and 11 which are not implicated in cervical cancer, but are responsible for over 90% of genital warts, and contribute to low grade cervical abnormalities.

Cervarix™ is a bivalent vaccine (two antigens) with a novel adjuvant, which may enhance the immune reponse.

Clinical trials show that both vaccines are effective and have excellent safety profiles. It is not yet clear whether the differences in formulation will result in any clinical differences in the long term.

Efficacy of vaccines

Combined clinical trial data (involving over 40,000 participants) has shown almost 100% efficacy against persistent HPV infection 16/18 in phase two studies of subjects with no previous exposure. Antibodies levels were 10–80 times higher than those observed in natural infection.[2-5] (N.B. The minimum serum antibody titre to protect from persistent HPV infection remains to be defined).

Efficacy is much lower when looking at outcomes among all subjects, regardless of previous exposure to HPV. In the Future 1 trial there was an efficacy of 20% for reduction

of grade 1–3 CIN or adenocarcinoma in situ (AIS), and this reduction was largely attributable to reduction in lower grade lesions.[6]

Promising early data on cross protection suggests there may be a 38% reduction in CIN2/3 or AIS caused by non-vaccine serotypes which contribute over 20% of cervical cancers.[7]

Duration of immunity

HPV prevalence and incidence peaks at approximately 20 years of age. This leads to peak incidence of CIN in the 25–30 year old age group, and cervical cancer from mid-life.[8] Therefore the duration of induced HPV immunity needs to be at least ten years after adolescent vaccination to protect against persistent HPV infection and subsequent development of CIN2/3.

Current evidence from clinical trials suggests sustained immunity up to five years with no evidence of waning.[9] Continued monitoring of longevity of immunity is underway.

Table 1: Comparison of commercial vaccines (randomised phase 2 studies) Adapted from Adams et al (2007)[1]

	Cervarix (GSK)	**Gardasil (Merck)**
HPV Types	16/18 high risk	16/18 high risk; 6/11 genital wart types
Expression system	Baculovirus	Yeast
Vaccination Schedule	0, 2 ,6 months	0, 1 ,6 months
Antigen dose	VLP 16, 18 (20, 20µg)	VLP 16,18,6,11(40, 20, 20, 40µg)
Adjuvant	ASO_4 [500µg $Al(OH)_3$+50µg MPL]	Alum 225µg[$Al(PO_4)$]
Trial size	560 vacinees; 553 placebo	227 vaccinees; 275 placebo
Trial countries	United States of America, Canada, Brazil	
Age, trial subjects	15–25 years	16–23 years
Duration of follow up	Up to 54 months	Up to 36 months
Efficacy (% CI intervals) (a) HPV infection Incident infection Persistent infection intention to treat (b) Cytological abnormalities (c) HPV 16/18 pre-malignancy	 96.9% (81.3–99.9) 94% (63–99) 97% (84–100) 100% (42–100)	 Not available 89% (73–96) Not published 100% (32–100)
Serious adverse events reported	Nil	Nil
Immune response (a) Seroconverson (b) Antibody titres	 100% 50–80 times natural infection	 100% 10–20 times natural infection

Safety of vaccines

These vaccines are both generally well tolerated with the most common adverse event being local discomfort at the injection site. There have been no discontinuations in trials due to adverse events, and serious adverse events were at similar rates to the placebo groups.

The clinical trial program for Gardasil vaccine safety involved subjects from 33 countries and safety data collected on more than 10,000 subjects aged 9 to 26 years, demonstrated that the vaccine was well tolerated. The most commonly reported adverse event in clinical studies was a mild local reaction at the injection site. Systemic reactions were also usually mild.

Published data on Cervarix also appears to show a good safety profile (data up to 4.5 years).[10]

Common issues with HPV vaccines

All sexually active women are at risk

HPV is very common, and while highly sexually active women are at higher risk of contracting HPV earlier, all sexually active women are at risk. A study found that the risk of HPV infection was 28.5% one year after first sexual intercourse, increasing to almost 50% by three years.[11]

Advice about practising safe sex should still be provided; it is important that women realise that the vaccine does not protect against all types of HPV or other sexually transmitted diseases.

There have been parental concerns expressed around adolescent HPV vaccine promoting promiscuity or earlier sexual activity. To date there is no evidence for this.

Vaccination most effective prior to sexual debut

There is currently no evidence that these vaccines have any therapeutic activity against persistent HPV infection. Consequently, for prophylactic vaccination to be most effective, it should occur prior to sexual debut.[8]

Age of vaccination

Early adolescent girls have been shown to have a better serological response to the HPV vaccine compared with older women. This could theoretically lead to longer lasting immunity.[9] However there is no definite evidence of this.

For women over 25 years the benefit of HPV vaccine is not clear, however there is likely to be benefit for a small group of women who may not have been exposed to infection. The potential benefit of vaccinating women who have successfully eradicated HPV infection with their own natural immunity to prevent re-infection occurring in late life is unknown.

Vaccination advice for the older teenager/young adult

It is difficult to predict the effectiveness of vaccinating for any sexually active individual as it is unclear if they have already acquired the specific HPV serotypes. However it can be expected that many older teenagers/young adults (and possibly older adults as well) would gain from being vaccinated. As the vaccination appears to have a good safety profile there is likely to be more to gain than to lose by offering vaccination to currently sexually active individuals, even when it is unclear of their HPV status.

Vaccination of males

The added value of vaccinating males to attempt herd immunity is currently not clear. Mathematical modelling to date suggested there is little added advantage if HPV vaccination coverage in the female population exceeds 70%.[12]

Potential effect of HPV vaccine on Cervical Screening

HPV vaccination in adolescence with continued cervical screening is projected to ultimately lead to a 76% lifetime reduction in cervical cancer deaths and 50% reduction in cervical screening abnormalities if high vaccination coverage is achieved.[1] In New Zealand there are approximately 30,000 abnormal smear results annually.

If early adolescent girls are vaccinated it will take at least 15 years before a major significant impact on the incidence of CIN2/3 will be seen, and at least 30 years before an impact on cervical cancer is seen.

Cervical screening will need to continue in the presence of a vaccination programme, firstly because there will be a large cohort of women who have been exposed to HPV prior to the onset of a vaccination programme who need surveillance, and because the vaccine does not protect against all types of oncogenic HPV.

Summary

HPV vaccination can be expected to reduce cervical cancer and possibly a range of other orogenital cancers. Vaccines appear to have good safety profiles to date, and duration of immunity is at least five years with ongoing monitoring.

Effectiveness is highest if given to females prior to exposure to HPV; hence the best age to deliver this vaccine is expected to be in the early adolescent period. An HPV vaccine is expected to be introduced soon into the New Zealand vaccination schedule for 11 year old girls. Currently neither vaccine is funded and costs approximately $400–$500.

There are significant implications for community awareness and education around the role of HPV in cervical cancer, the fact that it is a sexually-transmitted disease, and sustaining an ongoing high-quality cervical screening programme.

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