Landmark Review

The FUTURE Trial Programme

Quadrivalent vaccine against Human Papillomavirus (HPV) types 6, 11, 16 and 18

About the contributing specialists –

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Specialist Opinion – Dr Min K. Lo

The most significant features that make the Future I and Future II studies[3,5] a landmark study include:

- The studies involved more than 15,000 women aged 15 to 26 years at 90 sites in 13 countries in both the developed and developing world.
- They had a long follow up period of three years
- The trials were "real life" and included subects who already had a history of abnormal cervical cytology, infection or disease associated with HPV before being vaccinated or did not complete the three vaccinations.

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About Research Review

Research Review is an independent medical publishing organisation producing electronic journals. These journals provide summaries of ten 'must see' studies from the most respected medical journals in the world.

This and other Research Review publications are intended for New Zealand medical professionals.

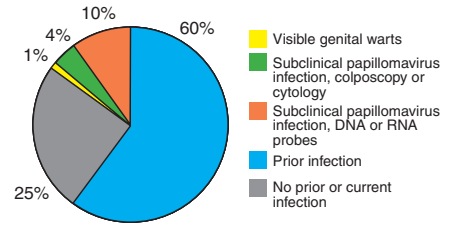
Background

Genital infection with the HPV is very common, occurring in around 75% of sexually active adults at some stage. In women, it is most prevalent amongst those of a younger age. Persistent infection with an oncogenic strain of HPV is associated with the development of almost all cervical cancers and is the most important risk factor for the development of their precursor abnormalities, cervical intraepithelial neoplasia (CIN) grades 2 or 3. An HPV 16 infection which persists for 5 years carries a risk of CIN 3 of up to 40%. However, CIN 2 and 3 can also develop rapidly, within a few months of infection.[1]

Around 70% of cervical cancers are related to infection with HPV types 16 and 18. Oncogenic HPV infection is also associated with cancer of the vulva, vagina, anus, penis and oropharynx.[2] Cervical cancer is the second most common cancer in women,[3] and is a leading cause of cancer morbidity and mortality.[2] It is estimated that without screening, around 11 in every 1,000 New Zealand women would develop cervical cancer, and that around 5 of them would die from it. With regular (3-yearly) screening, these figures are reduced to 2 and 1 respectively.[4]

Non-oncogenic HPV infection, particularly types 6 and 11, is associated with the development of genital warts.[2,3] These lesions are common, with US data suggesting an overall prevalence of around 1%.[1] Accurate population data are not available for New Zealand, however it is known that 3,822 new cases were diagnosed by sexual health clinics in 2004,[2] and recent studies in Australia and New Zealand have found incidences of between 3 and 12% in women.[1] Although they rarely progress to cancer, visible genital warts can be uncomfortable and unsightly, causing both physical and psychological distress. [1]

Estimated prevalence of genital HPV infection among men and women 15-49 years of age in the US (1994)



Current management of HPV infection

The New Zealand national cervical screening programme was set up in 1990. All women aged 20 to 70 are encouraged to have regular (3-yearly) PAP smears in order to help reduce the number of women who develop and die from cervical cancer. [4]

No treatment for subclinical HPV infection is advocated since the infection may spontaneously resolve. However women should receive repeat cervical screening as per the national guidelines. [1]

Treatment of genital warts, (which may include topical treatments, cryotherapy, diathermy, laser treatment or surgical removal) is required in cases where warts cause physical or psychological symptoms. It should be noted that treatment may not end the underlying HPV infection, and that warts may reappear post-treatment in around 1 in 3 patients. [1]

Current guidelines suggest that women who are diagnosed with CIN-1 or other low grade squamous intraepithelial lesions, and who have had no previous abnormalities, should have a second smear at 6 months, and be referred for colposcopy if this is also abnormal. If the lesion is high grade (CIN 2 or 3), referral for colposcopy should be immediate. If required, treatment consisting of either ablative therapy, excision biopsy or hysterectomy can be completed following colposcopic examination and biopsy. [7]

About the FUTURE trial programme

The efficacy and safety of a prophylactic quadrivalent HPV type 6,11,16,18 vaccine (Gardasil®) in preventing anogenital disease associated with HPV infection has been assessed in 2 large, randomised, controlled, double-blind trials. The results of the FUTURE (Females United To Unilaterally Reduce Endo/Ectocervical Disease) I and II trials were published in the New England Journal of Medicine in May 2007. [3,5]

The designs of both trials were similar, but varied with respect to their endpoints. Both assessed the efficacy of the vaccine in preventing cervical intraepithelial neoplasia (CIN) grade 2 or 3, adenocarcinoma in situ, or invasive cervical cancer associated with HPV types 16 or 18. In addition, FUTURE I looked at these outcomes in relation to infection with HPV 6 and 11, and also assessed the incidence of genital warts, vulvar or vaginal intraepithelial neoplasia (VIN) or cancer associated with HPV 6,11, 16 or 18.

The FUTURE I trial

Garland SM et al.
Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases.
N Engl J Med 2007;356:1928-43

Study design & methods

This was a phase III, international multi-centre, placebo-controlled, double-blind trial. Subjects were 5,455 healthy women aged 16 to 24 who were not pregnant and who had no prior history of genital warts or cervical abnormalities and no more than 4 previous sexual partners. Vaccination with quadrivalent HPV type 6,11,16,18 vaccine or placebo was given at day 1, month 2 and month 6.

At day 1 a full gynaecological examination was given, swabs were collected for anti-HPV and HPV DNA testing following a comprehensive anogenital examination, and a cervical sample was taken for Papanicolaou (PAP) cytologic testing. Follow-up assessments occurred at months 7, 12, 24, 36, and 48. HPV testing also occurred at month 3.

Primary outcome measures

The predefined primary endpoints were the incidence of genital warts, vulvar or vaginal intraepithelial neoplasia or cancer, cervical intraepithelial neoplasia, adenocarcinoma in situ, or cancer associated with HPV types 6, 11, 16, or 18.

Efficacy analysis

For HPV types 6, 11, 16 and 18, at least 99.5% of the subjects in the relevant per-protocol immunogenicity cohort had seroconversion at 1 month after the third dose.

The study populations for each of the efficacy analyses and their outcomes are detailed below. Average follow-up was 3 years following the first vaccination. In each group participants were included even if results of cytological tests from day 1 were abnormal.

Per-protocol susceptible population

Designed to assess the prophylactic efficacy of quadrivalent HPV type 6,11,16,18 vaccine under optimal conditions, this group comprised subjects who:

- Received all 3 doses of vaccine or placebo within 12 months and had no major protocol violations, and
- Were negative for HPV types 6, 11, 16 or 18 (serological and DNA analyses) at day 1 and remained so until 1 month after the 3rd dose

Quadrivalent HPV type 6,11,16,18 vaccine was 100% effective (95% CI, 94 to 100) in preventing vulvar, perineal, and perianal intraepithelial lesions or warts associated with HPV types 6, 11, 16 or 18 in the per-protocol population (0 cases vs 60 for placebo).

Quadrivalent HPV type 6,11,16,18 vaccine was 100% effective (95% CI, 94 to 100) in preventing CIN grades 1 to 3 and adenocarcinoma in situ associated with HPV types 6, 11, 16 or 18 in the per-protocol population (0 cases vs 65 for placebo).

Unrestricted susceptible population

This analysis assessed the prophylactic efficacy of vaccination under variable vaccine dose intervals and comprised subjects who were negative for HPV types 6, 11, 16 or 18 (serological and DNA analyses) at day 1. Participants were included even if protocol violations occurred.

In this analysis vaccine efficacy was 95% for all anogenital or vaginal lesions combined (4 vs 81 cases), 98% for all cervical lesions combined (2 vs 8 cases), 91% for high grade vulvar or vaginal lesions (1 vs 11 cases) and 100% for adenocarcinoma (0 vs 6 cases).

Intention-to-treat general study population

This prespecified supplementary analysis demonstrated the population effect of vaccination. It included subjects with evidence of infection or disease associated with HPV types 6, 11, 16 or 18 on day 1 and participants were included even if protocol violations occurred.

In vaccinated subjects, the rate of any vulvar or vaginal perianal lesions against a vaccine-type HPV was 73% (95% CI, 58 to 83, 28 cases vs 102 for placebo), and the rate of cervical lesions was 55% (95% CI, 40 to 66, 71 cases vs 155 for placebo).

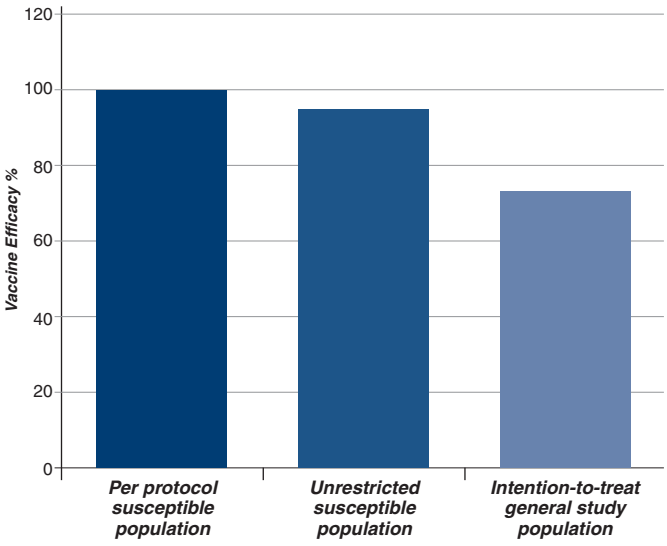
Tolerability

Pain, erythema, pruritis and swelling at the injection site were more common in the vaccine group compared to placebo. Fever (37.8 to 38.9°C) was reported by 13.3% of vaccine recipients compared to 10.3% of placebo recipients (Risk difference 3.0; 95% CI, 1.3-4.8). Rates of serious adverse events were similar in both groups.

Conclusions

Quadrivalent HPV type 6,11,16,18 vaccine effectively prevents the development of lesions resulting from infection with HPV types 6, 11, 16 and 18. These data suggest that widespread vaccination of young women and adolescent girls should result in a reduced incidence of cervical and external anogenital disease associated with HPV 6, 11, 16 and 18 infection.

Comparison of vaccine efficacy against external anogenital, vaginal, and cervical lesions associated with vaccine-type HPV, between each pre-specified population



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The important points to note are :

- The quadrivalent HPV vaccine is both safe and highly effective (100%) in preventing the acquisition of HPV 6, 11, 16 and 18; it is best given to females prior to sexual exposure.
- HPV subtypes 6 and 11 cause 90% of external genital warts and 10% of low grade cervical abnormalities (LSIL).
- Genital HPV infections are common and the associated psychological impact should not be underestimated. Treatment of genital warts is often time consuming and distressing for patients.
- The highest prevalence is in young women (20-25% around age 20). Acquisition of HPV infection is high after becoming sexually active (average age ~16 years) with peak incidence in the early 20's.[8]
- The likelihood of exposure is related to number of lifetime sexual partners. In a large WAVE III study involving women aged 18 to 25, having more than three lifetime partners was independently associated with HPV infection.[9]
- The incidence of HPV infection is similarly high in young men.[10]

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The FUTURE II trial

Koutsky LA et al.
Quadrivalent vaccine against human papilloma virus to prevent high grade cervical lesions.
N Engl J Med 2007; 356:1915-27

Study design & methods

This phase III international multi-centre, randomised, placebo-controlled, double-blind trial enrolled 12,167 subjects. Participants were healthy young women aged 15 to 26 years who were not pregnant, had no prior history of cervical abnormalities and no more than 4 previous sexual partners. Trial vaccine (Quadrivalent HPV type 6,11,16,18 vaccine) or placebo was given at day 1, month 2 and month 6.

Day 1 assessments included a full gynaecological and comprehensive anogenital examination. Swabs were collected for anti-HPV and HPV DNA testing, and a cervical sample was taken for Papanicolaou (PAP) cytologic testing. Follow-up assessments occurred at months 7, 12, 24, 36, and 48.

Primary outcome measures

The primary end point was CIN grade 2 or 3, adenocarcinoma in situ or invasive carcinoma of the cervix in the presence of DNA from HPV 16, 18 or both.

Efficacy analysis

In an immunogenicity sub-study of 1512 vaccinated women, more than 99% had seroconversion to the relevant vaccine-type HPV.

The study populations for each of the efficacy analyses and their outcomes are detailed below. Average follow-up was 3 years following the first vaccination.

Per-protocol susceptible population

As in FUTURE I, this analysis assessed the prophylactic efficacy of Quadrivalent HPV type 6,11,16,18 vaccine under optimal conditions. Subjects had negative PCR and serological tests for HPV 16 or 18 at baseline and remained negative until at least 1 month following the last dose. Subjects must have received all three doses of vaccine within 1 year and had no protocol violations.

In the per-protocol susceptible population, Quadrivalent HPV type 6,11,16,18 vaccine was 98% effective (95% CI, 86 to 100) for the prevention of CIN grade 2 or 3, adenocarcinoma in situ or invasive carcinoma of the cervix associated with HPV 16 or 18 infection (1 vs 42 cases).*

Unrestricted susceptible population

This analysis included all participants who had negative PCR and serological results for HPV types 16 or 18 on day 1 in order to provide an estimate of vaccine efficacy in a population with less than perfect compliance. More than 99% of subjects ultimately received the full 3-dose vaccination schedule.

The efficacy of Quadrivalent HPV type 6,11,16,18 vaccine in this group was 95% (95% CI, 85 to 99), with 3 vs 62 cases of CIN grade 2 or 3, adenocarcinoma in situ or invasive carcinoma of the cervix in the vaccine and placebo groups respectively.

Intention-to-treat general study population

The efficacy of Quadrivalent HPV type 6,11,16,18 vaccine on a population basis was estimated using an intention-to-treat analysis comprising all randomised subjects, regardless of baseline HPV and cervical neoplasia status.

Vaccine efficacy against lesions associated with vaccine-type HPV was 44% in the intention-to-treat group (95% CI, 26 to 58), with high grade cervical disease reported in 83 vaccinated subjects compared to 148 in the placebo group. Most lesions were associated with HPV 16 or 18 infection which was present at baseline and there was no evidence of a beneficial effect of vaccination on the progression of these lesions.

* For detailed explanation of the single case in vaccine group, see results section of full published paper. [3] pg 1920.

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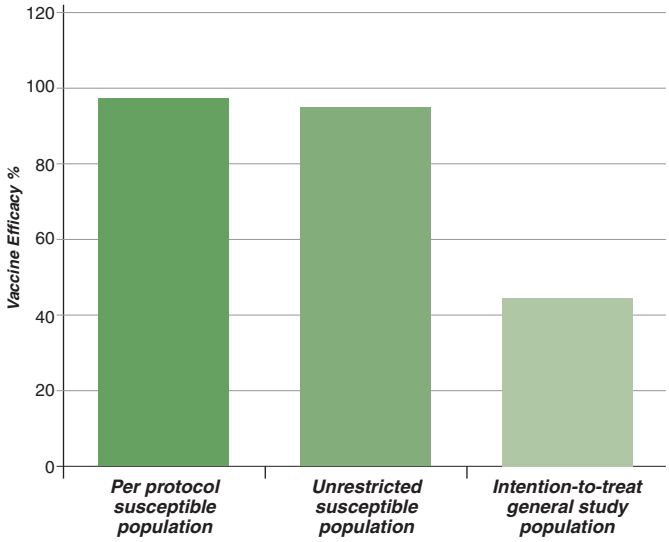
Comparison of vaccine efficacy against cervical intraepithelial neoplasia grade 2 or 3 or adenocarcinoma in situ associated with HPV-16 or HPV-18, between each pre-specified population.



A description of the 3 populations assessed in the efficacy analysis:

Analysis of prophylactic efficacy under optimal conditions (prespecified primary analysis)	**Per-Protocol Susceptible Population** Defined as subjects who: – Received all 3 doses of vaccine or placebo within 12 months – Were seronegative and HPV DNA negative on PCR analysis for HPV-6, HPV-11, HPV-16, or HPV-18 at day 1 – Remained negative on PCR analysis for the same HPV type (to which they were negative at day 1) through 1 month after the third dose – Had no major protocol violations – Were included even if results on cervical cytologic examination at day 1 were abnormal
Analysis of prophylactic efficacy under variable vaccine dose intervals (prespecified supplementary analysis)	**Unrestricted Susceptible Population** Defined as subjects who: – Were seronegative and HPV DNA negative on PCR analysis for HPV-6, HPV-11, HPV-16, or HPV-18 at day 1 – Were included even if protocol violations were present – Were included even if results on cervical cytologic examination at day 1 were abnormal
Analysis of population effect among all vaccinated subjects (prespecified supplementary analysis) (subjects may be positive for vaccine-type HPV DNA or have vaccine-type HPV antibodies)	**Intention-to-Treat General Study Population** Defined as subjects who: – Were included even if they had infection or disease associated with HPV-6, HPV-11, HPV-16, or HPV-18 (i.e. cervical intraepithelial neoplasia, vulvar intraepithelial neoplasia, or vaginal intraepithelial neoplasia) before vaccination – Were included even if protocol violations were present – Were included even if results on cervical cytologic examination at day 1 were abnormal

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Tolerability

Overall there were few adverse events associated with vaccination. Of those adverse events reported, events related to the injection site accounted for 84.4% of vaccinated subjects compared to 77.9% of those who received placebo. Injection site pain was the most commonly reported event in vaccinated patients (risk difference 6.5%, 95% CI, 1.4 to 11.7). Rates of serious adverse events were low and similar between groups (0.7 vs 0.9% for vaccine vs placebo).

Conclusions

The authors of this study concluded that quadrivalent HPV type 6,11,16,18 vaccine is highly effective in preventing high-grade cervical lesions associated with HPV 16 or 18 infection. They suggest that widespread vaccination may result in a decrease in cervical disease associated with these strains of HPV, including cervical cancer.

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How does the information from FUTURE I and II translate to the individual who is seeking an informed decision? Even if a woman is sexually active, she is likely to gain some benefit from receiving the vaccination. The quadrivalent vaccine provides protection against other HPV subtypes that the individual may not have been exposed to yet.[11]

There are ongoing studies to support the use of the vaccine in males as this will obviously decrease the burden of HPV disease in men and transmission of HPV to women.

As HPV becomes a more topical subject, it is important that doctors are able to effectively address patients' concerns and provide them with the appropriate information. The current Guidelines for the Management of Genital HPV were recently published in May 2007 and is available from www.hpv.org.nz

Specialist Opinion – Professor Ron Jones:

We now have definitive studies on the quadrivalent vaccine which confirm the efficacy demonstrated in preliminary studies. In addition, the efficacy of this quadrivalent vaccine is seen not only in the prevention of HPV-related cervical cancer precursors but also in HPV –related vaginal, vulval, perianal intraepithelial lesions or warts associated with the vaccine type.

Around 60,000 women in 35 countries, including New Zealand, have been involved in trials of the HPV vaccines with at least 5 years of safety data that indicate no long-term risks or loss of effectiveness.

The National Cervical Cancer Screening Program has achieved a 40% reduction in the incidence of cervical cancer and a 60% reduction in death rate over the past decade. However, 80% of women developing cervical cancer in New Zealand today have a suboptimal screening history. Maori have disproportionately high rates of disease. The vaccine will prevent more disease and deaths. It has the potential to provide protection for 30,000 young New Zealand women each year from the viruses which lead to cervical and other HPV -related cancers. About 180 New Zealand women are diagnosed with cervical cancer each year and about 60 die from the disease.

Registered use for quadrivalent HPV type 6,11,16,18 vaccine

Quadrivalent HPV type 6,11,16,18 vaccine is indicated for the prevention of cervical, vulvar and vaginal cancer, precancerous or dysplastic lesions, genital warts and infection caused by HPV (types 6, 11 & 18) in females aged 9 to 26 years. In males aged 9 to 15 years, quadrivalent HPV type 6,11,16,18 vaccine is indicated for the prevention of infection caused by HPV (types 6, 11 16 & 18). [6]

Quadrivalent HPV type 6,11,16,18 vaccine is not currently reimbursed under the New Zealand Government's vaccine programme.[2]

For more information on indications see **www.medsafe.govt.nz**

For information on cervical cancer vaccine reimbursement see the NZ Government's vaccine programme **www.moh.govt.nz/moh.nsf/pagesmh/4617/$File/2006-19newvaccines.pdf**

For more information on the cervical cancer screening programme see **www.nsu.govt.nz/Current-NSU-Programmes/564.asp**

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