

Landmark Review

The FUTURE Trial Programme

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

About the commentators -

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Dr Holt founded medical trials company P3 Research which has its head office in Wellington and a trial centre in Tauranga. Dr Holt has conducted over 50 clinical trials, mostly in respiratory medicine and has over 50 publications in medical literature. He is also an advisor to the Asthma and Respiratory Foundation, an Honorary Fellow of the Medical Research Institute of New Zealand and the principal advisor to Research Review.

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About Research Review

Research Review is an independent medical publishing organization producing monthly electronic journals including Respiratory Research Review, Diabetes & Obesity Review, Internal Medicine Review and GP Review. These journals provide monthly summaries of ten 'must see' studies from the most respected medical journals in the world together with a local specialist commentary indicating why they matter.

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:

- It is a combined analysis of four placebo controlled double blinded randomised trials
- 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.
- The studies had a long follow up period of 3 years
- The trials were "real life" and included subjects 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.

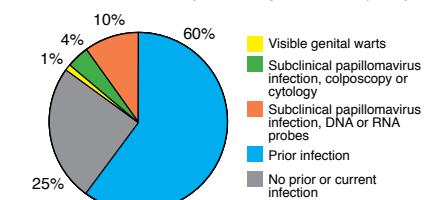
Background

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 II or III. An HPV 16 infection which persists for 5 years carries a risk of CIN III of up to 40%. However, CIN II and III 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 II or III), 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 human papillomavirus 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.

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, GARDASIL 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 Governments vaccine programme.²

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

For information on cervical cancer vaccine reimbursement see the NZ Government vaccine programme [www.moh.govt.nz/moh.nsf/pagesmh/4617/\\$File/2006-19newvaccines.pdf](http://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

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 Gardasil 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 Gardasil vaccination 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

Gardasil vaccination 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).

Gardasil vaccination 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.

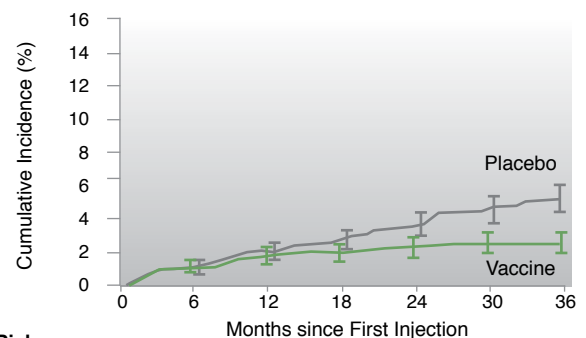
In vaccinated subjects (regardless of causal HPV type), the rate of any vulvar or vaginal perianal lesions was reduced by 34% (95% C, 15 to 49), and the rate of cervical lesions was reduced by 20% (95% CI, 8 to 31).

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

Gardasil vaccination 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.



No. at Risk	0	6	12	18	24	30	36
Vaccine group	2723	2562	2505	2443	2382	2293	1249
Placebo	2723	2566	2497	2419	2345	2249	1222

Cumulative No. of Subjects with an End Point	0	30	46	51	59	66	66
Vaccine group	0	30	46	51	59	66	66
Placebo	0	30	53	70	94	115	131

CIN Grade 1, 2, 3, or worse associated with HPV type 6, 11, 16 or 18 infection. (Intention-to-treat population)

Specialist Opinion - Dr Min K. Lo continued

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.⁹
- 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

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 (Gardasil) 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, 13, 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 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 Gardasil vaccination 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, Gardasil vaccination 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 HCV 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 Gardasil vaccination 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 Gardasil vaccination 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 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

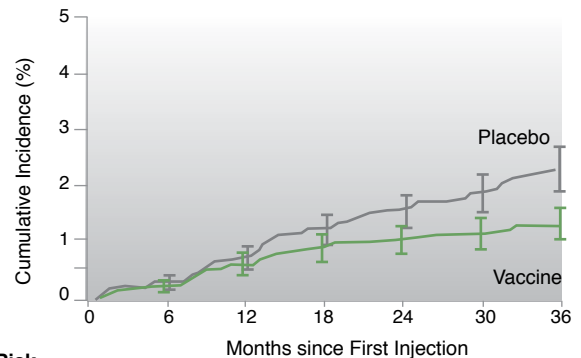
with HPV 16 or 18 infection which was present at baseline and there was no evidence of a beneficial effect of vaccination on the progression of these lesions.

Tolerability

Overall there were few adverse events associated with vaccination. Adverse events at the injection site were reported in 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).

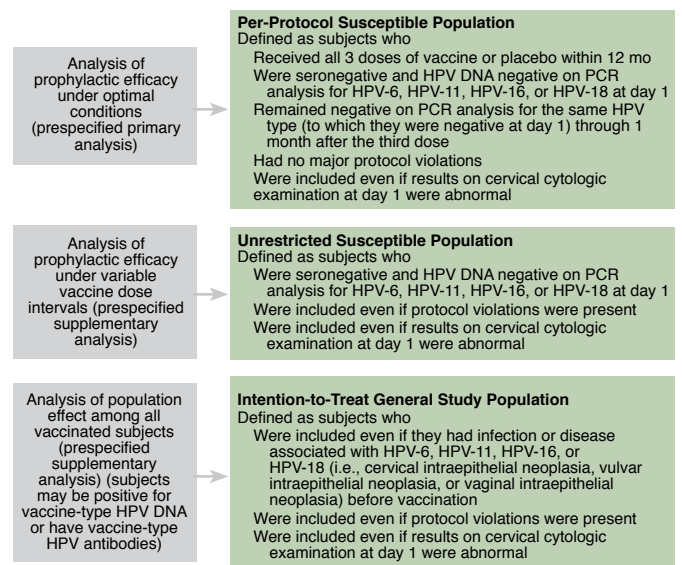
Conclusions

The authors of this study concluded that Gardasil vaccination 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.



No. at Risk	0	6	12	18	24	30	36
Vaccine group	6087	5918	5824	5733	5592	5427	2925
Placebo	6080	5942	5832	5736	5586	5420	2994
Cumulative No. of Subjects with an End Point							
Vaccine group	0	13	36	53	61	67	76
Placebo	0	17	43	72	91	109	132

Time until the development of high-grade cervical disease associated with HPV-16 or 18 infection (Intention-to-treat population).



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

Landmark Review - The FUTURE Trial Programme

Specialist Opinion Dr Min K. Lo continued:

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.

Commentary

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