How effective is the Human Papilloma Virus Vaccine?

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Abstract

A review of several research papers that present findings from prominent clinical trials reveals that the current quadrivalent HPV6/11/16/18 vaccine demonstrates high efficacy against Human Papilloma Virus (HPV) related cervical cancer. This research supports the implementation of a HPV vaccination programme. With such a programme in place, the incidence of HPV16/18 related cervical cancer would be profoundly reduced.

Introduction

Cervical carcinoma is the largest cause of cancer death among women in developing countries and second among women internationally. It has been well documented that Human Papilloma Virus (HPV), enhances the risk of developing cervical cancer[1]. HPV is the most common sexually transmitted disease and contracting HPV can be greatly increased by exhibiting unsafe sexual behaviour[1]. Developing and distributing a vaccination against HPV provides an opportunity to considerably decrease the incidence of cervical cancer worldwide.

In New Zealand there is a sizeable public health need for an HPV vaccine and there are significant disparities between Maori and non-Maori concerning the rates of HPV and cervical cancer. Age standardised incidence of cervical cancer among Non- Maori New Zealand women was 8.2 per 100,000 in 1999[2]. The incidence of cervical cancer seen in Maori was approximately double these figures, 16.0 per 100,000[2]. Also Maori cervical cancer related mortality is four times that of Non-Maori[2]. In light of these disturbing figures the National Cervical Screening Programme (NCSP) encouraged women to have two smears, twelve months apart when they turn 20 years old, then a smear every three years until they reach 70, provided that the findings of their smears remain normal[2]. Due to the implementation of this initiative there has been a 22% reduction in the incidence of cervical cancer and cervical cancer related deaths in all New Zealand women, but there are still inequalities seen between the rates for Maori and non-Maori[2]. In conjunction with this already established screening programme, an HPV vaccine has the potential to considerably reduce the incidence of HPV related cervical cancer among New Zealand women.

There have been more than a hundred different HPV genotypes discovered and these can be classified into low or high-risk categories in terms of their carcinogenic ability. There are four main genotypes that are targeted by the quadrivalent vaccine HPV6/11/16/18. Two of the genotypes are low grade HPV6 and HPV11. These produce benign genital warts (condyloma accuminata). The others are high grade HPV genotypes, HPV16 and HPV18, which together account for 70% of the major pathological agents contributing to cervical cancer[3]. Developing and distributing a vaccine that incorporates these four main HPV genotypes will be a significant step towards reducing the incidence of HPV-related cervical cancer.

Vaccine efficacy

The efficacy of the HPV vaccine is best demonstrated by the meta-analysis undertaken and presented by Dr Kevin A. Ault[4]. This research combined the findings of four separate randomised control trials. These trials involved 20,583 women between the ages of 16 and 26. Participants were randomly divided into three groups. Two groups were treated with one of two vaccines, either the quadrivalent vaccine HPV6/11/16/18 "Gardasil" or the HPV16/18 vaccine "Cervarix". The third group received a placebo[4]. All participants underwent periodic Papanicolaou testing and when an abnormality was detected a colposcopy or biopsy was carried out[4]. The vaccine efficacy was determined by observing the incidence of HPV16/18 related cervical intraepithelial neoplasia (CIN), adenocarcinoma in situ (AIS) and cervical cancer[4].

The data from the results of these trials was collected three years after the first dose of vaccine was administered. In women who were negative for HPV16 or HPV18 infection during the vaccination regimen, vaccine efficacy was determined to be 99%. It was also found that 85 women developed histologically confirmed HPV16/18-related CIN or AIS in the placebo group, in comparison only one case of HPV16-related CIN among the group who were allocated the HPV vaccine[4]. In an intention-to-treat analysis of all participants involved, including those who were naïve to HPV16/18 and those who were HPV16/18 infected, the vaccine efficiency was found to be 44%[4]. It has been determined as a consequence of these findings that the quadrivalent HPV vaccine is to be administered as a means of prophylactic treatment rather than providing a cure to those women already infected with the virus. This study provides strong evidence that the implementation of HPV vaccination in pre-adolescent girls and young adult women will profoundly reduce rates of cervical cancer worldwide.

Author & publication & year	Method	Study group and type	Findings
The Future II Study Group[5] New England Journal of Medicine 2007	Participates receive three doses of either HPV-6/11/16/18 vaccine or placebo, administered at day 1, month 2, and month 6.	Randomised, double blind trial. 12,167 women aged 15- 26 years assigned into vaccine group (6087) or placebo group (6080).	**Cases of HPV16/18 related CIN or AIS in restricted population:** 1 case in vaccine group, 42 cases in placebo group **Vaccine efficacy:** 98% **Cases of HPV16/18 related CIN or AIS in unrestricted population:** 3 cases in vaccine group, 62 cases placebo. **Vaccine efficacy:** 95% **Cases of HPV16/18 related CIN or AIS in modified ITT population:** 83 cases in vaccine group, 148 in placebo group. **Vaccine efficacy:** 44%
Villa LL et al.[7] Lancet Oncology 2005	Participates receive three doses of either HPV 6/11/16/18 vaccine or one of two placebo preparations, administered at day 1, month 2 and month 6.	Randomised, double-blind placebo-controlled phase II study. 1158 women aged 16-23 years, assigned into vaccine group (277) or one of two placebo groups (275).	**Efficacy of quadrivalent vaccine against persistent infection or disease associated with HPV 6, 11, 16, or 18:** 90% (95% CI 71–97, p<0·0001) **Efficacy of quadrivalent HPV vaccine against persistent infection or disease associated with HPV 6, 11, 16, or 18 in modified ITT analysis:** 89% (95% CI 73–96, p<0·0001)
Mao C et al.[8] Obstetrics & Gynocology 2006	Participates received three doses of either 40μg HPV16 L1 VLP vaccine or placebo, administered intramuscularly at day 1, month 2 and month 6.	Randomized, double-blind, placebo-controlled trial 2,391 women, aged 16-23 years, assigned into vaccine group (755) or placebo group (750).	**Cases of HPV16-related CIN:** 0 cases in vaccine group, 12 cases in placebo group. **Vaccine efficacy:** 100% (95% CI 65–100). **Cases of persistent HPV16 infection:** 7 cases in vaccine group, 111 cases in placebo group. **Vaccine efficacy:** 94% (95% CI 88–98).
Garland SM et al. [6] New England Journal of Medicine 2007	Participates received three doses of HPV6/11/16/18 or placebo administered at day 1, month 2 and month 6.	Randomised, double blinded, control trial. 5455 Women aged 16-24 years , assigned into vaccine group (2723) or placebo group (2732).	**Cases of HPV16/18 related CIS or AIS in per-protocol susceptible population:** 0 cases in vaccine group, 60 cases in the placebo group. **Vaccine efficacy:** 100% (95% CI, 88-100) **Cases of HPV16/18 related CIS or AIS in modified ITT analysis:** 104 cases in the vaccine group, 157 cases in the placebo group **Vaccine efficacy:** 34% (95% CI, 15-49)
Ault KA.[4] The Lancet 2007	Participates received three doses of either HPV6/11/16/18 vaccine, HPV16 vaccine or placebo, administered at day 1, month 2 and month 6.	Double-blind, placebo-controlled, randomised trials including a combined analysis of four randomised clinical trials. 20 583 women, aged 16-26 years were randomised to receive HPV6/11/16/18 vaccine (9087), its HPV16 vaccine component (1204), or placebo (10 292).	**Cases of HPV16/18-related CIN or AIS in pre-protocol susceptible population:** 1 case in vaccine group, 85 cases placebo group. **Vaccine efficacy:** 99% (95% CI 93-100). **Cases of HPV16/18-related CIN or AIS in unrestricted susceptible population:** 3 cases in vaccine group, 121 in placebo group. **Vaccine efficacy:** 98% (95% CI 93-100). **Cases of HPV16/18-related CIN or AIS in ITT population:** 142 cases in vaccine group, 255 in placebo group. **Vaccine efficacy:** 44% (95% CI 31-55)

Table 1. Displaying findings on HPV vaccine efficacy from five main clinical research trials: HPV-Human Papilloma Virus, CIN-Cervical intraepithelial neoplasia, AIS- adenocarcinoma in situ, ITT- intension-to-treat.

Limitations

While the results from the current HPV vaccine are encouraging, it is also important to recognize the limitations associated with the administration of the vaccine and the vaccine itself. The issues include the fact that even though the current HPV vaccine protects against two HPV genotypes which together account for 70% of all HPV related carcinogenic agents, it fails to include all aetiological determinants of cervical carcinoma[5]. Another limitation associated with the current HPV vaccine is that it does provide protection against HPV for naïve individuals but does not eradicate existing HPV infections[5]. Further concern surrounding this vaccine is that vaccinating against HPV is a recent development and the duration of protection of the vaccine and the required length of protection to prevent cervical cancer is information that is not yet available[5].

There are also practical limitations which include the cost and administration of the three dose regimen, and the possible need for an additional booster injection[5]. These practical concerns will most certainly limit the number of individuals receiving vaccinations, especially in countries where the rate of HPV is high, but follow up health care is inadequate and a vaccine is yet to be subsidised[5]. However the benefits of the HPV vaccine most certainly out weigh the limitations, but these factors need to be considered carefully because they directly influence the efficacy of the HPV vaccine.

Ethical issues

Although comprehensive vaccination provides the most effective means of reducing the incidence of cervical cancer, mandatory HPV vaccination raises several ethical and social issues of concern. HPV is a common sexually transmitted disease, so infection by the virus can be successfully prevented with abstinence and also by the use of condoms[6]. One of the most frequently discussed concerns is that vaccination against HPV may result in the promotion of reckless sexual behaviour and premature sexual activity among adolescents. There is not substantial evidence to support these assumptions however these concerns can be minimalised through appropriate education[6]. Education will ensure that the vaccination against HPV is perceived, by the health profession and the general public, as a prophylactic measure rather than something that would promote promiscuity[6].

Conclusion

Cervical carcinoma is the largest cause of cancer deaths among women in developing countries and second among women internationally. Extensive studies have demonstrated that developing and distributing the current prophylactic quadrivalent vaccine HPV6/11/16/18, has the potential to reduce the incidence of HPV related diseases among women worldwide and also here in New Zealand. The current HPV vaccination programme has some practical and ethical issues that need to be considered, as they have the potential to influence the efficacy of the vaccine. These issues are outweighed, however, by the benefits that this vaccine presents. Currently being researched is the link between HPV and other cancers such as rectal, penile, and oropharyngeal. This then raises the possibility of immunising males against HPV in the future. Implementing a vaccine that safeguards against cervical cancer provides the first step towards reducing the incidence of other HPV related diseases.

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