

# The potential impact of mass HPV vaccination on cervical cancer prevention: population and clinical perspectives

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Cancer of the cervix is the second most common cancer in women worldwide, with about 500,000 new cases and 250,000 deaths each year. The greatest burden of cervical cancer is found in underserved, resource-poor populations where almost 80 percent of cases occur, and where cervical cancer is the most common cancer in women.<sup>1</sup>

By contrast, cervical cancer prevention initiatives, namely population-based screening programmes, have been highly successful in many developed countries, achieving high reductions in both incidence and mortality from cervical cancer.<sup>2</sup> In New Zealand, since the introduction of a nationally coordinated Cervical Screening Programme in 1990, there has been a 50 percent reduction of cervical cancer incidence, and a 65 percent reduction in mortality, which can be attributed largely to cervical screening.<sup>3</sup>

Human papillomavirus (HPV) is one of the most common viruses infecting humans. It is sexually transmitted and highly infectious. It infects a high proportion of men and women within a few years of sexual activity. Most HPV infections are asymptomatic, therefore most infected people are unaware they are infected, yet they can transmit the infection to a sexual partner.

Persistent cervical infection with one of 15 to 18 'high risk' types of HPV causes virtually all invasive cervical cancer.<sup>4</sup> HPV type 16 is reported to be the most common oncogenic HPV type, detected in about 50 percent of high grade abnormalities and invasive cervical cancers worldwide. HPV type 18 is detected in about 15 percent of invasive cervical cancers. HPV 18 is found in a greater proportion of adenocarcinomas than squamous cervical cancers. Other oncogenic types contributing to the burden of cervical cancer include types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 73 and 82.<sup>5 6 7</sup>

Two HPV vaccines have recently become available:

- a quadrivalent vaccine (Gardasil, Merck & Co) which covers oncogenic HPV types 16 and 18, as well as HPV types 6 and 11, non oncogenic types that cause genital warts
- a bivalent vaccine (Cervarix, GlaxoSmithKline) which covers HPV types 16 and 18 only.

Gardasil has been approved by Medsafe for use in New Zealand for women aged 9-26 years, and is available through general practice. Licensing of Cervarix is still under consideration in New Zealand but has recently been approved for use in Australia for women aged 10 to 45 years. While HPV vaccines represent a potential valuable approach to cervical cancer prevention, several experts have recommended that the following concerns should be addressed prior to a mass population based vaccination programme roll out:<sup>8 9 10</sup>

- the current vaccines do not prevent cervical cancer caused by all HPV 'high risk' genotypes, only types 16 and 18. It is currently unknown what proportion of

cervical cancer in New Zealand can be attributed to HPV types 16 and 18, although this is unlikely to be higher than 70 percent at the most

- the vaccines cannot prevent cancer in women who have already been infected with HPV types 16 and 18. Therefore vaccination must be given before the age at which females tend to become sexually active, ideally around the age 11 years
- the duration of immunity to HPV 16 and 18 is uncertain at present and still needs to be determined by long-term follow up of vaccinated subjects. The vaccine studies to date have only lasted for four to five years
- there is no data at present regarding the required frequency of booster doses, or even if boosters will be required at all. This is an important cost consideration
- it is not clear whether any cross protection exists against other high-risk genotypes and therefore the maximum protective effect is unlikely to exceed 70 percent
- immunisation of boys is likely to be required to ultimately break the cycle of transmission and achieve herd immunity. Long-term studies in boys are required before mass vaccination can be offered to males as well as females
- while the vaccines appear to be relatively well tolerated in the trials, with reactions being mainly local, long term safety of these vaccines can only be determined from surveillance over many years
- there is a potential for these vaccines to increase inequalities if underserved and unscreened populations do not achieve vaccination coverage at least as high as their less deprived groups
- lack of knowledge about HPV infection and its effects are key barriers to vaccine acceptance. A clearly focused public education campaign will be mandatory for acceptance of a mass campaign.

There is a possibility that as vaccination reduces the circulation of types 16 and 18, other less common oncogenic virus types will evolve to occupy the ecological niche left by the former types. Long term surveillance should identify such changes.

As vaccinated cohorts reach screening eligibility age, it may be possible to lengthen the screening interval and age range but this is unlikely to occur for many years to come. Therefore the operational costs of the NCSP are unlikely to change for some time to come.

Mass vaccination should ultimately reduce the occurrence of abnormal smears (LSIL and HSIL) and referral of women to colposcopy. Reductions in the rates of smear abnormalities and colposcopies will make it more difficult for laboratories and colposcopists to maintain quality (which depends on minimum volumes) and this could impact negatively on the screening programme in the years to come.

By far the greatest risk for women is that those who have been vaccinated, and even those who have not, may mistakenly believe that cervical cancer is no longer a problem and will be less conscientious about turning up for regular cervical smears.

Neither screening nor vaccinating alone is ever likely to prevent all cases of cervical cancer, but a contribution from both is likely to provide the best protection.

Before vaccination can be introduced however, the issues outlined above need to be thought through and the cost effectiveness of screening plus vaccinating versus screening alone needs to be quantified for New Zealand.

The most important message for all women in the meantime, whether they choose to be vaccinated against HPV 16 and 18 or not, is that they will need to participate in

regular cervical screening. If women become less conscientious about getting regular smears, vaccination could potentially lead to an increase in cervical cancer at the population level, despite providing some protection for some women at the individual level.

#### **HPV vaccination issues still to be resolved:**

- When should girls be vaccinated?
- Should boys be vaccinated as well?
- Should an initial 'catch up' be offered for older girls/young women?
- Will boosters be needed, and if so when?
- Will there be any cross protection against oncogenic genotypes not included in the vaccine types other than 16 and 18?
- Will other oncogenic genotypes evolve to replace types 16 and 18?
- What proportion of girls (and boys) will actually accept the vaccine and how will this differ by ethnic and socioeconomic group?
- Will vaccination lead to widening of inequalities and cervical cancer incidence/mortality between ethnic groups and socioeconomic groups?
- Will the vaccine be taken up largely by the seam women who would have attended regularly for cervical screening? In this case, little impact (if any) on cervical cancer rates is to be expected.
- How will we prevent vaccination leading to a deterioration in the screening programme as laboratories and colposcopists will no longer be able to maintain minimum volumes and hence expertise?
- Most importantly, will vaccination lead to an increase rather than a decrease in cervical cancer rates if women mistakenly believe they are no longer at risk and so become less conscientious about having cervical smears?

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<sup>1</sup> World Health Organisation. 2006. Preparing for the introduction of HPV vaccines: policy and programme guidance for countries

<sup>2</sup> International Agency for Research on Cancer (IARC). Handbook of cancer prevention. Vol 10. Lyon, France. IARC 2005

<sup>3</sup> NZHIS Cancer Statistics

<sup>4</sup> Parkin DM. 2006. The global burden of infection associated cancers in the year 2002. *Int J Cancer* 118:3030-3044

<sup>5</sup> Munoz N et al. 2003. Epidemiological classification of human papillomavirus types associated with cervical cancer. *N Eng J Med* 348:518-527

<sup>6</sup> Stanley M. Prophylactic HPV vaccines: prospects for eliminating ano-genital cancer. *British Journal of Cancer* 2007. 96 1320-1323

<sup>7</sup> MMWR. Recommendations of the Advisory Committee on Immunisation Practices. March 23, 2007/Vol56/RR-2

<sup>8</sup> Baden LR et al. Human Papillomavirus Vaccine – Opportunity and Challenge. *NEJM* 2007. 356;1990-1991

<sup>9</sup> Gostin L et al. Mandating HPV vaccination. Public Health vs Private Wealth. *JAMA* 2007. 297;1921-1923

<sup>10</sup> Savage L. Proposed HPV Vaccine mandates Rile Health Experts Across the Country.. *JNCI*. 2007.