

19 New Vaccines

19.1 Human papilloma virus

Introduction

Human papilloma virus (HPV) vaccines are now in stage III clinical trials. The pharmaceutical companies expect to apply for licensure overseas, and in Australia and New Zealand in 2006.

Human papilloma virus vaccine

Two vaccines against HPV have been developed and are in stage III clinical trials. One is a bivalent vaccine, containing HPV types 16 and 18, the other quadrivalent, containing HPV types 16, 18, 6 and 11. HPV-6 and 11 are not oncogenic but can cause florid genital warts. The pharmaceutical companies are expecting to apply for licensure in the United States (US), Australia and New Zealand in 2006.

Illness and epidemiology

Cervical cancer is one of the leading causes of cancer morbidity and mortality in women throughout the world. Prior infection with oncogenic HPV is a necessary although not sufficient prerequisite for the development of cervical cancer. Infection with oncogenic HPV types is also implicated in the development of other anogenital cancers, including neoplasms of the vulva, vagina, anus, penis and oropharynx. Non-oncogenic HPV types cause genital warts. Of the oncogenic HPVs, types 16 and 18 account for some 70% of cervical cancers; the remainder are caused by a variety of other oncogenic HPV types, for example, types 31, 33 and 45. HPV infection is common with an estimated 70 percent of sexually active women becoming infected.¹ International studies have shown that HPV-16 infection is the type most commonly associated with cervical cancer and is found in about 60 percent of cervical cancers. This is followed by HPV type 18, found in about 10 percent of cervical cancers.

Cervical screening programmes are based on regular cytological screening to detect, monitor and treat at an early stage precancerous lesions, or cervical intraepithelial neoplasia (CIN). These programmes have been successful in reducing invasive disease and mortality.

A vaccine to prevent infection with oncogenic HPV types has the potential to reduce the incidence of precursor lesions and cervical cancer². However, vaccination needs to be administered before HPV infection occurs. Since genital HPV is so common, this means vaccination before the onset of sexual activity – realistically, during early adolescence.

The stage III trial results are encouraging and suggest an HPV vaccine may be effective in preventing persistent HPV infection and therefore may prevent the development of cervical cancer. Further information is needed from ongoing studies

to define the duration of protection and the optimal timing for the vaccine. It will be important to analyse the effect of the HPV vaccine on the design of cervical screening programmes over a woman's lifetime, and economic models may be useful³ in examining the options.

New Zealand epidemiology

Both cervical cancer incidence and mortality have fallen dramatically in New Zealand (as in other developed countries) over the last decade, due to cervical screening. New Zealand's National Cervical Screening Programme, administered by the National Screening Unit of the Ministry of Health, became operational in 1991 and now achieves over 70 percent coverage of eligible women (ie, the 20–69 year age range).

Over the past 10 years cervical screening has led to a 40 percent reduction in the incidence of invasive cervical cancer. However, incidence remains approximately twice as high among Māori than among non Māori women. Over the same period, mortality from cervical cancer has fallen about 60 percent. Again, ethnic inequalities remain, with mortality among Māori still approximately 4 times that of non Māori. Much of the ethnic inequality in the cervical cancer burden reflects lower Programme coverage for Māori women (approximately 55 percent compared to 75 percent).

In New Zealand, the cervical screening programme has led to a reduced incidence of invasive disease and has facilitated recall. The National Cervical Screening Register records the woman's cytological reports and results of investigations, and sends out recalls for three-yearly cervical screening.

One source of information on the incidence of HPV infection in New Zealand comes from surveillance data collected from sexual health clinics, youth health clinics and some family planning clinics. These data are collated and analysed by the Institute of Environmental Science and Research (ESR). In 2004 there were 3822 new diagnoses of genital warts in males and females in sexual health clinics; population rates cannot be calculated. The age group most affected by genital warts is young adults aged 15–24 years. The number of new cases seen has increased over time, although some of the increase may represent changes in presentation at clinics rather than a change in incidence.

An Auckland study⁴ of 513 cervical swabs, mainly from women attending colposcopy clinics, found that 221 specimens (43 percent) were positive for HPV. Twenty-two different types of HPV were detected, and 141 were oncogenic types, representing 14 of the 18 known oncogenic types. Types 16, 18, and 31 were the most common detected, representing 39 percent, 10 and 10 percent of the oncogenic types found, respectively. The other 11 oncogenic HPV types ranged in prevalence from 7.4 to 0.6 percent.

In considering options for timing an HPV vaccine for the immunisation schedule in New Zealand, it is useful to consider the results of the 2001 Youth Health Survey,⁵ which provides information on sexual behaviours. Among secondary school students in years 9 to 13, 17 percent of students aged 13 years reported they had had sexual intercourse, 33 percent of those aged 15 years, and 49 percent of students aged 15 years.

Vaccines

There are two vaccines currently in stage III clinical trials. One vaccine is bivalent with HPV- types 16 and 18, and the other is a quadrivalent vaccine with HPV types 16, 18, 6 and 11. Trials are underway studying the vaccine in young women, women up to age 45 years and in males.

Both vaccines under trial are recombinant and contain HPV L1 virus like particles (VLPs). The VLPs mimic the true structure of the virion and induce an antibody response after vaccination. An earlier HPV-16 vaccine showed protection against persistent infection with HPV-16 and associated CIN.⁶

Bivalent vaccine: HPV-16,18 virus like particle vaccine (Cervarix, GSK)

The bivalent HPV-16,18 vaccine manufactured by GSK contains 20 µg of HPV-16 L1 VLP and 20µg of HPV-18 L1 VLP. Each type of VLP was produced on *Spodoptera frugiperda* Sf-9 and *Trichoplusia ni* Hi-5 cell substrate with AS04 adjuvant containing 500 µg of aluminium hydroxide and 50 µg 3-deacylated monophosphoryl lipid A.

In a randomised controlled trial⁷ in North America and in Brazil, three doses of this bivalent vaccine, or a placebo, were given to 1113 women aged between 15 and 25 years at zero, one month and six months. The women were seronegative for HPV-16 and 18 at the study's commencement.

Of the women receiving the vaccine, 100 percent seroconverted to the HPV-16 and 99.7 percent seroconverted to HPV-18. Geometric mean titres (GMT) for naturally occurring infections are 50 ELISA units/mL for HPV-16, and 41 ELISA units/mL against HPV-18. The GMT of the women who received the vaccine were over 80 and 100 times greater than after natural infection with HPV-16 and 18, and the titres remained high at 18 months (10 to 16 times higher than after natural infection). The study found that the vaccine was highly efficacious in preventing incident and persistent HPV-16 and 18 infections in the fully vaccinated women. Efficacy against persistent infection with HPV-16, 18 was assessed as 100 percent in the according to protocol cohorts (95% confidence interval [CI]: 47–100). There was a 91.6 percent efficacy against incident infection (95% CI: 64.5–98.0) after 18 months follow up, which persisted at 27 months. Two women in the vaccine group developed HPV-16 and/or HPV-18 associated cytological abnormalities; one developed low grade squamous intraepithelial lesion and the other developed atypical squamous cells of undetermined significance. This compared with 27 women in the placebo group who developed lesions.

Expected reactions and adverse events following immunisation (AEFI) with the bivalent HPV vaccine (GSK)

The bivalent HPV-16,18 vaccine was safe and well tolerated. No serious adverse events were reported in the trial. Local reactions were common, with 34.3 percent of vaccine recipients reporting swelling and 35.6 percent redness at the injection site; 93.4 percent reported pain. Other symptoms reported following vaccination were gastrointestinal, headache, itching and rash. No temperatures over 39°C were reported, although 16.6 percent of vaccine recipients reported a temperature of over 37.5°C.

Quadrivalent vaccine: HPV-6,11,16,18 virus like particle vaccine (GARDASIL, Merck)

This quadrivalent vaccine now manufactured by Merck is based on technology developed by CSL.

Studies involving adult women

The pre-publication results of stage III vaccine trials in women after 17 months of follow up were announced in 2005.⁸ The study enrolled 12,167 women in 90 centres around the world, and women were randomised to receive three doses of the HPV vaccine or placebo. The vaccine was 100 percent effective (95% CI: 76–100) in preventing high grade cervical pre-cancers, and non-invasive cervical cancers (CIN 2/3 and adenocarcinoma in situ [AIS]), in 17 months of follow up after completing the course of vaccine. No cases of AIS or CIN 2 or 3 were reported in women who had received three doses of GARDASIL, compared to 21 cases in the control group.

An earlier stage II study compared 275 women who received a placebo to 276 women who received the quadrivalent vaccine,⁹ which contained 20 µg HPV type 6, 40 µg type 11, 40 µg type 16, and 20 µg of HPV type 18. The women were followed for 30 months, and the study found a 90 percent decrease of HPV 6, 11, 16 or 18 infection, or genital disease in the vaccine recipients. This study showed that the low dose vaccine, with levels of antigen as above gave comparable immunogenicity to the intermediate and high dose vaccine. There were 40 endpoints of HPV detection in the trial participants, of which four were in the vaccine group. These were: at the last recorded visit at 36 months, three women in the vaccine group had HPV 16 DNA detected in cervicovaginal sample, compared with 10 women with HPV 6, 11, 16 or 18 in the placebo group. One woman in the vaccine group had HPV 18 detected at 12 and 18 months only. The estimated efficacy of the vaccine against all four HPV types was 89 percent (95% CI: 73–96). At month 36, 94 percent of the vaccine recipients were seropositive for HPV type 6, 96 percent for HPV type 11, 100 percent for HPV type 16, and 79 percent for HPV type 18.

Studies involving adolescent males and females, and young women

The results of a non-inferiority study in 1016 adolescent males and females aged 10 to 15 years and 513 young adult women aged 16 to 23 years were presented in 2005.¹⁰ Participants received the quadrivalent vaccine at zero, two and six months. To demonstrate non-inferiority, serology tests on day one and at month seven for serum anti-HPV antibodies on the adolescent study subjects were to be comparable with the results for the young women and the results of a previous study on adult women.¹¹

At month seven the seroconversion rates for the girls and boys were 100 percent for anti-HPV-6, 11, and 16, and 99.6 percent for anti-HPV-18. The month seven geometric mean titres (GMT) were 1.67–2.7 times higher (non-inferior, $p < 0.001$) than in the young adult cohort. Anti-HPV-6, 11, 16 and 18 GMTs in boys were 1.07–1.33 times higher than the GMTs in girls.

These results in young adolescents prior to sexual activity support the bridging of efficacy data from studies in adult women. Which is to say, if the GMT and seroconversion rates in adolescents are comparable to adult women, then efficacy in adolescents may be inferred from the efficacy in studies of adult women, without lengthy clinical trials in adolescents being necessary for licensure. This finding is important because the vaccine is likely to be of most benefit if given before the initiation of sexual activity, and this study is the first demonstration of seroconversion in adolescent males.

Expected reactions and adverse events following immunisation (AEFI) with the quadrivalent HPV vaccine (Merck)

The quadrivalent vaccine was well tolerated. Pain at the injection site was the most common local reaction, and overall 86 percent of vaccine recipients reported injection site reactions. Headache was the most common systemic reaction, and overall 38 percent of vaccine recipients reported systemic symptoms. Most reactions (94 percent) were mild or moderate. There were no vaccine related serious adverse events.

Immunisation schedule for HPV vaccines

Three doses of vaccine are given. In the reported trials the following schedules were used.

- The bivalent HPV-16,18 vaccine (Cervarix, GSK) was given at zero, one month and six months.
- The quadrivalent HPV-16,18,6,11 vaccine (GARDASIL™, Merck) was given at zero, two months and six months.

19.2 Rotavirus

Introduction

Rotavirus gastroenteritis is a significant cause of infant diarrhoea worldwide, both in developed and in less developed countries. In less developed countries rotavirus is a common cause of mortality, and in developed countries is a cause of hospitalisations.

Illness

Rotavirus causes diarrhoea in infants between the ages of six and 24 months. Accompanying symptoms include vomiting and fever, and the illness lasts from three to eight days. The virus is present in the stool before the development of symptoms and may persist for up to 21 days.

Transmission occurs through the faecal-oral route. In severe cases of rotavirus infection dehydration and electrolyte imbalance may occur, and in immune compromised children and children with human immunodeficiency virus (HIV) infection may become chronic.

Most children will have been infected by the age of three years. Breastfed infants may also become infected with rotavirus but the illness is milder. Adults are infected through contact with infected infants, although most adults will have no symptoms. The incubation period ranges from two to four days.

The rotaviruses are segmented, double stranded RNA viruses of the family Reoviridae. There are seven distinct antigenic groups (groups A to G). Group A viruses are the commonest, causing disease worldwide, but groups B and C are also important in human disease. The virus is also classified into serotypes based on two outer capsid proteins the VP7 (G protein) and VP4 (P protein). Types G1–4 and 9, and P type 1A and 1B are the most common.

Vaccines

The types of virus assessed for use as rotavirus vaccines have included live attenuated virus, both human and animal strains of the virus, as well as human-animal reassortant viruses developed for vaccines. A recent summary has described the progress in rotavirus vaccines and the information below is taken from this paper.¹²

An oral human-rhesus rotavirus quadrivalent vaccine (Rotashield, Wyeth) was licensed in the US and on the infant schedule in 1999. It was voluntarily withdrawn from the market after reports of an association of this vaccine with intussusception. Other vaccines assessed have been a human-lamb vaccine used in some parts of China, and vaccines with human-bovine strains. Others have been studied, with differing results, in developed and developing countries. The vaccines Rotateq and Rotarix are the most likely to be available first in developed countries.

Pentavalent WC3 - based bovine - human reassortant vaccine (Rotateq, Merck)

This vaccine contains five bovine–human reassortants representing the common VP7 types, G1–4 and P(8). The vaccine is administered as a three-dose oral course at the same time as the usual infant schedule. In large trials the vaccine had an efficacy of 74 percent against all disease, and 98 percent against severe disease. A large safety trial found no evidence of intussusception.

Monovalent human G1 rotavirus vaccine (Rotarix, GSK)

Rotarix is a monovalent G1 rotavirus vaccine derived from a human G1 strain. The vaccine is given in two oral doses at the same time as the usual schedule vaccines. In trials the efficacy was reported as 72 percent and 85 percent against all and severe disease. Further trials have confirmed good efficacy, and the vaccine was licensed in 2004 in Mexico and the Dominican Republic, and licensure is now being sought in many other countries. The safety trials showed no evidence of intussusception.

Information on the immunisation schedules for these rotavirus vaccines will be available at a later date.

References

- 1 Villa LL, Costa LR, Petta CA, et al. 2005. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. *Oncology. The Lancet*; on line April 7 2005. DOI 10.1016/S1470-2045 (05) 70101-7.
- 2 Frazer IH. 2004. Prevention of cervical cancer through papillomavirus vaccination. *Nature Reviews Immunol* 4: 46-54
- 3 Kulasingham SL, Myers ER. 2003. Potential Health and Economic Impact of Adding a Human Papilloma Vaccine to Screening Programs. *JAMA* 290: 781-9.
- 4 Thomas SM, Croxson MC. 2005. *Genital Papillomavirus Genotypes in Auckland, New Zealand*. Poster presentation at 22nd HPV Conference 2005.Vancouver, Canada.
- 5 Adolescent Research Group. 2003. A health profile of New Zealand youth who attend secondary school. *NZ Med J*; 116: 1171-2. URL: <http://www.nzma.org./journal/116-1171/380>.
- 6 Koutsky LA, Ault KA, Wheeler CM, et al. 2002. A controlled trial of a human papillomavirus type 16 vaccine. *N Engl J Med* 347: 1645-51.
- 7 Harper DM, Franco EL, Wheeler C, et al. 2004. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet* 364: 1757-65.
- 8 Koutsky LA. 2005. Prophylactic Quadrivalent Human Papillomavirus (HPV) (Types 6,11,16,18) L1 Virus-Like Particle (VLP) Vaccine (Gardasil™) Reduces Cervical Intraepithelial Neoplasia (CIN) 2/3 Risk. Information from CSL information release. October 2005.
- 9 Villa LL, Costa RLR, Petta CA, et al. 2005. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. *Oncology. The Lancet* on line April 7 2005. DOI 10.1016/S1470-2045 (05) 70101-7.