

HPV vaccine (Gardasil®) – potential concerns explained

This document aims to address some of the potential concerns which have been raised in various forums about the vaccine against Human Papillomavirus (HPV), called Gardasil® by providing up to date factually accurate information. This has been prepared so that teenagers, parents, care givers and health professionals can make an informed decision based on factual information.

The following topics are provided as background information:

- Cervical cancer in New Zealand
- Why is a vaccine against HPV viruses needed?
- What HPV vaccines are available in New Zealand?

This explanatory document will then go on to address some of the ‘potential concerns’ which have been promoted in some internet and print forums. In particular, it will clarify the inaccuracies around the following statements:

- The vaccine (Gardasil®) will not treat pre-existing infection and increases the risk.
- The vaccine (Gardasil®) has not been evaluated for carcinogenicity, genotoxicity, or pregnancy.
- The vaccine (Gardasil®) causes birth defects.
- The vaccine (Gardasil®) only protects against only four strains of the HPV virus.
- The long-term effectiveness of the vaccine (Gardasil®) is unknown.
- The placebo vaccine used in the clinical studies included aluminium, which is reactive, so the safety picture of Gardasil® may be inaccurate.
- The vaccine (Gardasil®) is still in the testing stage and 18 people have died.
- The males in the community will infect the girls.

At the end of the document is an appendix where you will find information that may be of interest:

- What are the risk factors for cervical cancer?
- What is a clinical trial?
- What is the Immunisation Advisory Centre?
- What is the Immunisation Awareness Society?
- What is Judicial Watch (USA)?

Cervical cancer in New Zealand

- In New Zealand, approximately 160 women develop cervical cancer each year and about 60 women die from it.
- Cervical cancer usually develops very slowly, taking up to ten or more years to develop. It starts when some cells on the surface of the cervix become abnormal. These abnormal cells may return to normal by themselves but in a small number of cases, they may develop into cancer if not treated.
- Vaccines can now be used to prevent cervical cancer.

Why is a vaccine against HPV viruses needed?

- Genital HPV viruses are an extremely common infection (a type of wart virus) that is usually sexually transmitted. To develop cervical cancer a woman must contract certain types of HPV.
- Most sexually active people will acquire genital HPV, the majority within the first 2 years of onset of sexual activity. In a small percentage of women the virus stays around, and over many years leads to the development of cancer, most commonly caused by HPV types 16 and 18.
- Most people will never know that they have this virus.
- Most of the time, HPV goes away on its own. When HPV is gone, the cervical cells go back to normal. But sometimes, HPV does not go away. Instead it lingers (persists) and continues to change the cells on a woman's cervix. These cellular changes can lead to cancer over time, if they are not treated.
- Cervical screening detects these abnormalities and most can be treated before the cellular changes become cancer.
- HPV related abnormalities of the cervix generally require surgical treatment.
- HPV vaccines are highly effective at preventing the most common genital HPV infections and therefore preventing HPV related cellular changes and cancer developing.
- Most external visible warts are caused by HPV types 6 and 11, and these types do not cause cervical cancer. However these types may be troublesome and can also be prevented by vaccination.

Website for further information: www.hpv.org.nz

What HPV vaccines are available in New Zealand?

- There are two vaccines for preventing the most common HPV types associated with cervical cancer. Both vaccines have been tested in thousands of people in many countries, including NZ.
- Gardasil® immunises against HPV types 16 and 18, which can lead to approximately 70% of cervical cancers, and HPV types 6 and 11, which can lead to 90% of visible genital warts.

- Cervarix® immunises against types 16 and 18.
- Studies show that both Gardasil® and Cervarix® are highly effective (close to 100%) in preventing infection caused by these types of HPV.
- Vaccination with both Gardasil® and Cervarix® require three doses by injection spread over six months.
- Vaccination will not protect against all types of HPV that lead on to cancer, so women need to remain vigilant, and continuing with the cervical screening programme is also important

Website for further information: www.hpv.org.nz

Which vaccine is free on the HPV immunisation programme?

- Gardasil® is the HPV vaccine which is funded on the national immunization schedule.
- Cervarix® is a private purchase medicine. This means the vaccine needs to be paid for.
- From 2009 the HPV vaccine will be given to year 8 girls (age 12 and 13 years).
- A catch up programme started in September 2008 for girls aged 17-18.
- The catch up programme is being extended to girls aged 12-18 years in 2009 and 2010.

Website reference: [www.moh.govt.nz/moh.nsf/pagesmh/7891/\\$File/letter-healthproviders-hpv.pdf](http://www.moh.govt.nz/moh.nsf/pagesmh/7891/$File/letter-healthproviders-hpv.pdf)

Misleading Statements and responses:

One: The vaccine (Gardasil®) will not treat pre-existing infection and increases the risk

The potential concern:

Since Gardasil® does not cure HPV, persons who already had any lesions or symptoms from pre-existing strains were not counted in the study. This is problematic because many women have HPV without knowing it and Gardasil® does not require pre-screening before vaccination.

Statements have been made that the vaccine Gardasil® can make the disease worse in women who already have persistent infection with HPV. Furthermore individuals have suggested that women who already have the virus without knowing it could suffer massive outbreaks of genital warts or abnormal cancerous lesions.

The facts:

- The Gardasil® vaccine is designed to prevent cervical cancer resulting from HPV infection. It does not treat women who have already contracted the infection and it cannot cure women who are already developing cancer after being exposed to the virus.
- The Gardasil® vaccine contains 4 strains of HPV (types 16 and 18 which may lead to 70% of cervical cancers, and types 9 and 11, which are associated with 90% of genital warts)
- The women in the clinical studies fell into one of three categories:
 - Per protocol: These women had never been exposed to the strains of HPV contained in the vaccine before they started in the study and remained uninfected until one month after dose 3 was given. They received all 3 doses of vaccine. In this group the efficacy of the vaccine was 100% against the HPV types 16 and 18.
 - Modified intention to treat: These women included those who had never been exposed to the strains of HPV contained in the vaccine at the start of the study but either did not

Key messages:

- *Gardasil® is not a therapeutic vaccine, it is a prevention vaccine.*
- *Vaccination needs to be given prior to exposure to HPV (i.e. preferably prior to being sexually active).*
- *Combined data from all the clinical studies show no increased risk in worsening of pre-existing diseases.*

complete the 3 doses, or became infected with HPV prior to completing their course. In this group the efficacy of the vaccine was 98.8% against HPV 16 and 18.

- Modified intention to treat – general population: These included women who had already been infected prior to the start of the study and may have not completed the full course during the study period. In this group the efficacy of the vaccine was, perhaps not surprisingly, only 39%.
- Of course, cases of HPV infection due to other HPV types not covered by the vaccine are also seen as the vaccine does not cover against all HPV types.
- In one study (013) a small number of women who were had already been exposed to HPV virus 16 and/or 18 prior to starting the vaccination course did develop changes in the cervix by the end of the study. The numbers were small, 31 cases in the vaccine group and 19 cases in the placebo control group. Data from other studies, with larger numbers did not find an increased risk. Furthermore in the subgroup of women in the smaller study (013) other risk factors for cervical cancer, such as smoking, were higher in the Gardasil® group and could have influenced the outcomes.

Two: The vaccine (Gardasil®) has not been evaluated for carcinogenicity, genotoxicity, fertility or pregnancy

The potential concern:

Statements have been made that the scientists did not bother to study cancer.

The facts:

- Vaccine final formulations are exempt from carcinogenicity studies but have to undergo very strict safety evaluations in animals well before being given to humans. Carcinogenicity studies may be required for particular vaccine components.
- When applying for a license to conduct a clinical study in humans, there are 5 toxicology categories that have to be met before a license would be considered:
 - Intrinsic toxicology: All vaccine components are assessed in acute toxicology studies.
 - Toxicology studies are linked to pharmacodynamic (i.e. the biochemical and physiological effects of the vaccine) activity: checking for the potential for autoimmune reaction requires careful selection of the appropriate animal model.
 - Biological toxicology: Evaluating for any effect on existing autoimmune conditions.
 - Toxicology of contaminants or impurities: Ensuring absence of impurities is an essential criteria.
 - Evaluation of potential adverse reactions due to the interaction of vaccine components.
- All vaccines used in women of child bearing age are evaluated for embryo-fetal and post-natal toxicology:

Key messages:

- *All vaccines undergo very strict safety evaluations.*
- *Gardasil® underwent stringent toxicology tests and animal model studies.*
- *No harmful effects were identified when the vaccine was given prior to mating, during gestation, or during the lactation phase.*

- Gardasil® was assessed in animal models (rats) at three stages: prior to mating; during gestation; and during lactation.
 - The animals were given 300 times the human dose of Gardasil®.
 - No treatment related effects were identified.
- Antibodies against all 4 vaccine types of HPV were transferred to the offspring, both placental and through lactation.

Key messages:

- *In the combined studies there were equal rates of pregnancy in the vaccine group and placebo group.*
- *There were equal rates of live births in the vaccine group and the placebo group.*
- *There were equally low rates of congenital abnormalities in the vaccine group and placebo group.*

Three: The vaccine (Gardasil®) causes birth defects

The potential concern:

During clinical trials there were five cases of babies with congenital birth defects born to women who had the vaccine within 30 days of becoming pregnant. There were no such birth defects in the placebo group of women who had become pregnant within 30 days of receiving the placebo.

The facts:

- In the Phase III clinical studies, there were over 2000 subjects with pregnancies. Of these, 1115 were in the Gardasil® groups and 1151 were in the placebo groups.
 - The number of live births was approximately equal in both groups (621 in the Gardasil® group and 611 in the placebo group).
 - Fetal loss was similar in both groups (375 in Gardasil® and 407 in placebo).
 - Infant/fetal congenital anomalies were similar in both groups (15 in the Gardasil® group and 16 in the placebo group).
- In conclusion, there are no concerns on outcomes, if the Gardasil® vaccine is accidentally used in women who become pregnant.

Four: The vaccine (Gardasil®) only protects against 4 strains

The potential concern:

The vaccine only protects against 4 types of HPV even though there are over 30 different types at least 15 of which cause cancer.

The facts:

- The vaccine is targeted at the 2 types of HPV which are associated with 70% of cervical cancers (HPV 16 and 18) worldwide, plus the 2 types which are associated with 90% of genital warts (HPV 9 and 11).
- HPV 16 is identified with over 50% of cervical cancers and HPV 18 is identified with nearly 20%. Thus a vaccine containing these two strains covers 70% of the HPV types causing cervical cancer.
- By adding other HPV types, the protection would increase by only a few percent per type added. For example, the next two most common types (HPV 45 and 31) account for a further 10% of cases combined. The other HPV types contribute between 0.3%-2.6% each type.
- Worldwide, HPV types 6 and 11 cause 90% of genital warts. Although these warts do not cause cancer, they can be recurrent and difficult to treat.
- The primary purpose of the HPV vaccination programme is the prevention of cervical cancer.

Key messages:

- *The vaccine protects against the two strains that are thought to cause 70% of cervical cancer in NZ.*
- *The vaccine protects against the two strains that are thought to cause 90% of genital warts in NZ.*

Five: The long term effectiveness of the vaccine (Gardasil®) is unknown

The potential concern:

The long term effectiveness is unknown and could be too brief to be effective.

The facts:

- The key to long term immunity following vaccination is the stimulation of a robust antibody response and the induction of immune memory.
- The Gardasil® vaccine has not been around long enough to determine how long it will continue to prevent HPV infection. The longest follow up of women in the clinical studies is 5 years.
- Vaccination with Gardasil® has been shown to elicit a strong and stable antibody response, immune memory, and long term disease protection through at least 5 years.
- If an antigen challenge is given at the five-year point, there is a strong immune response to the challenge, showing there is still excellent immune memory in women who had received 3 doses of the vaccine 5 years ago.
- In summary; to date the data still looks good 5 years after the vaccine was given, with no sign of waning memory.
- There is no gold standard test for immunity to HPV. Disease prevention remains the most important measure of long term duration of vaccine efficacy.

Key messages:

- *Current data is available five years after immunisation showing there is still a high level of protection, good immune memory and no sign of waning protection.*
- *The clinical programme will continue to monitor the long term impact on cervical disease.*

Six: The placebo vaccine used in the (Gardasil®) clinical studies included aluminium, which is reactive, so the safety picture of Gardasil® may be inaccurate

The potential concern:

An additional safety report shows that Gardasil® was tested against an aluminium placebo with an undisclosed amount of aluminium in it. Using a reactive instead of a non-reactive saline base can make vaccines seem safer than they may be. Aluminium can cause permanent cell damage and is a reactive placebo, unlike most standard saline placebos. This means that tests of Gardasil® may not have given an accurate picture of safety levels.

Key messages:

- *Both aluminium and saline were used as placebo vaccines.*
- *The incidence of systemic reactions is very low in both groups.*
- *Aluminium is used in a number of vaccines and has a good safety record of over 70 years.*

The facts:

- The vaccine was also tested against a placebo that did not contain aluminum, only saline.
- Both the Gardasil® vaccine and the aluminium-containing placebo vaccine contained the same amount (225 mcg) of aluminium.
- Aluminium is well known to cause minor local reactions, such as pain at the site of injection.
- Aluminium use in vaccines has a safety record extending back over 70 years.
- The incidence of systemic reactions was very low in both groups.

For more information on aluminium in vaccines: <http://www.immune.org.nz/?T=722>

Seven: The vaccine (Gardasil®) is still in the testing stage and 18 people have died

The potential concern:

Statements have been made that Gardasil® is still in the 'testing stages', and will not be fully evaluated for safety until September 2009. Reports from the 'Vaccine Adverse Event Reporting System' (VAERS) show that as many as 18 people have died after using Gardasil®

The facts:

- Since 2003, the Gardasil® clinical programme has carefully studied an ethnic diversity of people from 33 countries including New Zealand.
- Gardasil® is registered (licensed for use) in a wide geographical spread of countries.
- Gardasil® is funded for use in national programmes in many countries including the majority of Europe, the Americas and Australasia.
- The safety profile is excellent with vaccine related serious adverse events occurring in <0.1% of persons (less than 1 per 1000).
- Adverse events occur in similar proportions in the vaccine and placebo group.
- There have been 10 deaths in the Gardasil® group and 7 deaths in the placebo group (there were more people in the vaccine groups therefore the proportions are equal).
 - The causes of death were mainly trauma (such as motor vehicle accident), 4 in the Gardasil® group and 3 in the placebo group.
 - No causal link has been shown between Gardasil® vaccination and any of the causes of death.

Key messages:

- Gardasil® has been carefully evaluated in large studies for 5 years.
- The vaccine is in wide use internationally with many millions of doses administered and monitored.
- There have been a small and similar number of deaths in both the placebo group and the Gardasil® group.
- No causal link has been found between Gardasil® vaccination and any cause of death.

Eight: The men in the community will infect the women.

The potential concern:

Since the HPV programme only vaccinates girls, concerns have been expressed that there may be no chance of reducing the circulation of the virus in the community and the HPV 16 and HPV 18 strains will still be out there just waiting until the girls' immunity wears off.

The facts:

- Men also carry the HPV virus and can infect women with the HPV virus strains through sexual activities. Always using a condom during sex can reduce a woman's risk of acquiring the virus however it is not fully protective.
- In women who are fully immunized prior to exposure, the efficacy of the vaccine is close to 100% against HPV 16 and HPV 18 which are associated with 70% of cervical cancer in NZ.
- Vaccination with Gardasil® has been shown to provide long term disease protection in women and girls, through at least 5 years.
- Most men who get HPV (of any type) never develop any symptoms or health problems however some types of HPV can cause genital warts. Other types can cause penile or anal cancer.
- Recent clinical trials in young men aged 16-26 show that the vaccine Gardasil® is effective in decreasing the incidence and persistence of infection with HPV 6/11/16/18 and HPV-related external genital warts. Further research is required to determine the long term place of HPV vaccine in men.

Key messages:

- *Always using a condom during sex reduces the risk of HPV transmission from boys to girls.*
- *Girls who are fully immunised against HPV will have a very high degree of protection for at least 5 years.*

REFERENCES

1. Block SL, Nolan T, Sattler C, Barr E, Giacoletti KE, Marchant CD, et al. Comparison of the immunogenicity and reactogenicity of a prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in male and female adolescents and young adult women. *Pediatrics* 2006;118(5):2135-45.
2. Bosch FX, Lorincz A, Muñoz N, Meijer CJLM, Shah KV. The causal relation between human papillomavirus and cervical cancer *Journal of Clinical Pathology* 2002;55:244-265.
3. Burd EM. Human papillomavirus and cervical cancer. *Clinical Microbiology Reviews* 2003;16(1):1-17.
5. Castellsague X, Munoz N. Chapter 3: Cofactors in human papillomavirus carcinogenesis--role of parity, oral contraceptives, and tobacco smoking. *Journal of the National Cancer Institute* 2003;Monographs.(31):20-8.
7. Collins S, Mazloomzadeh S, Winter H, Blomfield P, Bailey A, Young LS, et al. High incidence of cervical human papillomavirus infection in women during their first sexual relationship. *BJOG: An International Journal of Obstetrics & Gynaecology* 2002;109(1):96-8.
8. de Villiers E-M, Fauquet C, Broker TR, Bernard H-U, zur Hausen H. Classification of papillomaviruses. *Virology* 2004;324(1):17-27.
9. Fairley CK, Gay NJ, Forbes A, Abramson M, Garland SM. Hand-genital transmission of genital warts? An analysis of prevalence data. *Epidemiology & Infection* 1995;115(1):169-76.
10. Ferenczy A, Bergeron C, Richart RM. Human papillomavirus DNA in fomites on objects used for the management of patients with genital human papillomavirus infections. *Obstetrics & Gynecology* 1989;74(6):950-4.
11. Food and Drug Administration. Clinical Review of Biologics License Application for Human Papillomavirus 6, 11, 16, 18 L1 Virus Like Particle Vaccine (S. cerevisiae) (STN 125126 GARDASIL), manufactured by Merck, Inc. In: Vaccines Clinical Trial Branch DoVaRPA, Office of Vaccines Research and Review, Centre for Biologics Evaluation and Research, editor: Food and Drug Administration, 2006.
12. Future II Study Group. Prophylactic efficacy of a quadrivalent human papillomavirus (HPV) vaccine in women with virological evidence of HPV infection.[see comment]. *Journal of Infectious Diseases* 2007;196(10):1438-46.
13. Garland SM, Hernandez-Avila M, Wheeler CM, Perez G, Harper DM, Leodolter S, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases.[see comment]. *New England Journal of Medicine* 2007;356(19):1928-43.
14. Greer CE, Wheeler CM, Ladner MB, Beutner K, Coyne MY, Liang H, et al. Human papillomavirus (HPV) type distribution and serological response to HPV type 6 virus-like particles in patients with genital warts. *Journal of Clinical Microbiology* 1995;33:2058-2063.
15. Herrero R, Castellsague X, Pawlita M, Lissowska J, Kee F, Balaram P, et al. Human papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study. *Journal of the National Cancer Institute* 2003;95(23):1772-83.
16. Institute of Environmental Science and Research. Sexually Transmitted Infections in New Zealand. Annual Surveillance Report 2006. In: ESR, editor. Wellington, 2007.
17. Kashima HK, Mounts P, Shah K. Recurrent respiratory papillomatosis. *Obstetrics & Gynecology Clinics of North America* 1996;23(3):699-706.
18. Kjaer SK, Chackerian B, van den Brule AJ, Svare EI, Paull G, Walbomers JM, et al. High-risk human papillomavirus is sexually transmitted: evidence from a follow-up study of virgins starting sexual activity (intercourse). *Cancer Epidemiology, Biomarkers & Prevention* 2001;10(2):101-6.

19. Koutsky L. Epidemiology of genital human papillomavirus infection. *American Journal of Medicine* 1997;102(5A):3-8.
20. Koutsky LA, Ault KA, Wheeler CM, Brown DR, Barr E, Alvarez FB, et al. A controlled trial of a human papillomavirus type 16 vaccine. *New England Journal of Medicine* 2002;347(21):1645-51.
21. Manhart LE, Koutsky LA. Do condoms prevent genital HPV infection, external genital warts, or cervical neoplasia? A meta-analysis. *Sexually Transmitted Diseases* 2002;29(11):725-35.
22. Markowitz LE, Dunne EF, Saraiya M, Lawson HW, Chesson H, Unger ER, et al. Quadrivalent Human Papillomavirus Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morbidity & Mortality Weekly Report* 2007;Recommendations & Reports. 56(RR-2):1-24.
23. Merck & Co Inc. Recombivax HB® Hepatitis B Vaccine (Recombinant) prescribing information. Whitehouse Station, NJ, 1998.
25. Munoz N, Bosch FX, Castellsague X, Diaz M, de Sanjose S, Hammouda D, et al. Against which human papillomavirus types shall we vaccinate and screen? The international perspective.[see comment]. *International Journal of Cancer* 2004;111(2):278-85.
27. Roden R, Monie A, Wu TC. The impact of preventive HPV vaccination. *Discovery Medicine* 2006;6(35):175-81.
29. Thomas SM, Croxson MC. Genital Papillomavirus Genotypes in Auckland, New Zealand. (Poster presentation). *22nd HPV Conference 2005*. Vancouver, Canada., 2005.
30. Villa LL, Costa RL, Petta CA, Andrade RP, Ault KA, Giuliano AR, et al. 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. *Lancet Oncology* 2005;6(5):271-8.
31. Villa LL, Costa RL, Petta CA, Andrade RP, Paavonen J, Iversen OE, et al. High sustained efficacy of a prophylactic quadrivalent human papillomavirus types 6/11/16/18 L1 virus-like particle vaccine through 5 years of follow-up. *British Journal of Cancer* 2006;95(11):1459-66.
32. Winer RL, Lee SK, Hughes JP, Adam DE, Kiviat NB, Koutsky LA. Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students. *American Journal of Epidemiology* 2003;157(3):218-26.

APPENDICES

What are the risk factors for cervical cancer?

A risk factor is anything that changes your chance of getting a disease such as cancer. Different cancers have different risk factors. For example, exposing skin to strong sunlight is a risk factor for skin cancer. Smoking is a risk factor for many cancers. But having a risk factor, or even several, does not mean that you will get the disease.

Several risk factors increase your chance of developing cervical cancer. Women without any of these risk factors rarely develop cervical cancer. Although these risk factors increase the odds of developing cervical cancer, many women with these risks do not develop this disease. When a woman develops cervical cancer or pre-cancerous changes, it may not be possible to say with certainty that a particular risk factor was the cause.

In thinking about risk factors, it helps to focus on those that you can change or avoid (like smoking or catching human papilloma virus infection), rather than those that you cannot (such as your age and family history). However, it is still important to know about risk factors that cannot be changed, because it's even more important for women who have these factors to get regular Pap tests to detect cervical cancer early.

Cervical cancer risk factors include:

Human papilloma virus infection: The most important risk factor for cervical cancer is infection by the human papilloma virus (HPV). HPV is a group of more than 100 related viruses. They are called papilloma viruses because some of them cause a type of growth called a papilloma. Papillomas are not cancers, and are more commonly called warts. HPV is passed from one person to another during skin-to-skin contact. HPV can be spread during sex - including vaginal intercourse, anal intercourse, and even during oral sex.

Women must have been infected by HPV before they develop cervical cancer. Certain types of HPV are called "high-risk" types because they are often the cause of cancer of the cervix. These types include HPV 16, HPV 18, HPV 31, HPV 33, and HPV 45, as well as some others. About two-thirds of all cervical cancers are caused by HPV 16 and 18.

Different types of HPVs cause warts on different parts of the body. Some types cause common warts on the hands and feet. Other types tend to cause warts on the lips or tongue.

Still other types of HPV may cause warts on or around the female and male genital organs and in the anal area. These warts may barely be visible or they may be several inches across. The medical term for genital warts is *condyloma acuminatum*. Two types of HPV, HPV 6 and HPV 11, cause most cases of genital warts. These two types are seldom linked to cervical cancer, and so are called "low-risk" types of HPV. Other sexually transmitted HPVs have been linked with genital or anal cancers in both men and women.

Many women become infected with HPV, but very few will ever develop cervical cancer. In most cases the body's immune system fights off the virus, and the infection goes away without any treatment. For reasons that we don't understand, the infection persists in some women and can cause cervical cancer. Although there is currently no cure for HPV infection, there are ways to treat the warts and abnormal cell growth that HPV causes.

The Pap (cervical smear) test looks for changes in cervical cells caused by HPV infection.

HPV infections occur mainly in young women and are less common in women over 30. The reason for this is not clear. Uncircumcised men are thought to be more likely to have the virus and be able to pass it on to someone else. HPV infection can be present for years without any symptoms. Even when someone doesn't have visible warts (or any other symptom), he (or she) can still be infected with HPV and pass the virus to somebody else.

Condoms ("rubbers") do provide some protection against HPV, but they cannot completely protect against infection. This is because HPV can still be passed from one person to another by skin-to-skin contact with an HPV-infected area of the body that is not covered by a condom - like the skin in the genital or anal area. Still, it is important to use condoms to protect against AIDS and other sexually transmitted illnesses that are passed on through some body fluids.

Vaccines have been developed to help prevent infection with some types of HPV. Right now, there is an HPV vaccine that has been approved for use in the United States by the Food and Drug Administration (FDA). This vaccine is called Gardasil®, and it protects against HPV types 6, 11, 16, and 18. More HPV vaccines are being developed and tested.

Although it is necessary to have had HPV for cervical cancer to develop, most women with this virus do not develop cancer. Doctors believe that other factors must come into play for cancer to develop. Some of the known factors are listed below.

Smoking: Women who smoke are about twice as likely as non-smokers to get cervical cancer. Smoking exposes the body to many cancer-causing chemicals that affect more than just the lungs. These harmful substances are absorbed by the lungs and carried in the bloodstream throughout the body. Tobacco by-products have been found in the cervical mucus of women who smoke. Researchers believe that these substances damage the DNA of cervix cells and may contribute to the development of cervical cancer.

Immunosuppression: Human immunodeficiency virus (HIV), the virus that causes AIDS, damages the body's immune system and seems to make women more at risk for HPV infections. This may be what increases the risk of cervical cancer in women with AIDS. Scientists believe that the immune system is important in destroying cancer cells and slowing their growth and spread. In women with HIV, a cervical precancer might develop into an invasive cancer faster than it normally would.

Chlamydia infection: Chlamydia is a relatively common kind of bacteria that can infect the reproductive system. It is spread by sexual contact. Some studies have seen a higher risk of cervical cancer in women whose blood test results show past or current chlamydia infection (compared with women with normal test results). Infection with chlamydia often causes no symptoms in women. A woman may not know that she is infected at all unless she is tested for chlamydia when she gets her pelvic exam. Long-term

chlamydia infection can cause pelvic inflammation, leading to infertility.

Diet: Women with diets low in fruits and vegetables may be at increased risk for cervical cancer. Also overweight women are more likely to develop this cancer.

Oral contraceptives (birth control pills): There is evidence that taking oral contraceptives (OCs) for a long time increases the risk of cancer of the cervix. Research suggests that the risk of cervical cancer goes up the longer a woman takes OCs, but the risk goes back down again after the OCs are stopped. In a recent study, the risk of cervical cancer was doubled in women who took birth control pills longer than 5 years, but the risk returned to normal 10 years after they were stopped.

The American Cancer Society believes that a woman and her doctor should discuss whether the benefits of using OCs outweigh the potential risks. A woman with multiple sexual partners should use condoms to lower her risk of sexually transmitted illnesses no matter what other form of contraception she uses.

Multiple pregnancies: Women who have had many full-term pregnancies have an increased risk of developing cervical cancer. No one really knows why this is the case. One theory is this may be because some of the women may have been exposed more to HPV through un-protected sexual contact. Also, studies have pointed to hormonal changes during pregnancy as possibly making women more susceptible to HPV infection or cancer growth. Another thought is that the immune system of pregnant women might be weaker, allowing for HPV infection and cancer growth.

Low socioeconomic status: Poverty is also a risk factor for cervical cancer. Many women with low incomes do not have ready access to adequate health care services, including Pap tests. This means they may not get screened or treated for pre-cancerous cervical disease.

Diethylstilbestrol (DES): DES is a hormonal drug that was given to some women to prevent miscarriage between 1940 and 1971. Women whose mothers took DES (when pregnant with them) develop clear-cell adenocarcinoma of the vagina or cervix more often than would normally be expected. There is about 1 case of this type of cancer in every 1,000 women whose mothers took DES during pregnancy. This means that about 99.9% of "DES daughters" do not develop these cancers.

DES-related clear cell adenocarcinoma is more common in the vagina than the cervix. The risk appears to be greatest in women whose mothers took the drug during their first 16 weeks of pregnancy. The average age of women when they are diagnosed with DES-related clear-cell adenocarcinoma is 19 years. Since the use of DES during pregnancy was stopped by the FDA in 1971, even the youngest DES daughters are older than 35 - past the age of highest risk. Still, there is no age cut-off when these women are safe from DES-related cancer - doctors do not know exactly how long women will remain at risk.

'DES daughters' may also be at increased risk of developing pre-cancerous changes of cervical squamous cells and squamous cell cancer of the cervix. These pre-cancers and cancers seem to be linked to HPV.

Although 'DES daughters' have an increased risk of developing clear cell carcinomas, women don't have to be exposed to DES for clear cell carcinoma to develop. In fact, women were diagnosed with the disease before DES was developed.

Family history of cervical cancer: Cervical cancer may run in some families. If your mother or sister had cervical cancer, your chances of developing the disease are increased by 2 to 3 times. Some researchers suspect that some instances this familial tendency may be caused by an inherited condition that makes some women less able to fight off HPV infection than others. In other instances, women from the same family as a patient already diagnosed may be more likely to have one or more of the other non-genetic risk factors previously described in this section.

Ref: American Cancer Society
www.cancer.org/docroot/CRI/content/CRI_2_4_2X_What_are_the_risk_factors_for_cervical_cancer_8.asp
Last Revised: 03/26/2008

What are clinical trials?

In health care, clinical trials are conducted to allow safety and efficacy data to be collected for new drugs or devices. These trials can only take place once satisfactory information has been gathered on the quality of the product and its non-clinical safety, and Health Authority/Ethics Committee approval is granted in the country where the trial is taking place.

Depending on the type of product and the stage of its development, investigators enroll healthy volunteers and/or patients into small pilot studies initially, followed by larger scale studies in patients that often compare the new product with the currently prescribed treatment. As positive safety and efficacy data are gathered, the number of patients is typically increased. Clinical trials can vary in size from a single center in one country to multicenter trials in multiple countries.

There are five phases of clinical trials:

Pre-clinical studies involve in vitro (test tube) and in vivo (animal) experiments using wide-ranging doses of the study drug to obtain preliminary efficacy, toxicity and pharmacokinetic information. Such tests assist pharmaceutical companies to decide whether a drug candidate has scientific merit for further development as an investigational new drug.

Phase 0 is a recent designation for exploratory, first-in-human trials conducted in accordance with the U.S. Food and Drug Administration's (FDA) 2006 Guidance on Exploratory Investigational New Drug (IND) Studies.^[13] Phase 0 trials are also known as human microdosing studies and are designed to speed up the development of promising drugs or imaging agents by establishing very early on whether the drug or agent behaves in human subjects as was expected from preclinical studies. Distinctive features of Phase 0 trials include the administration of single subtherapeutic doses of the study drug to a small number of subjects (10 to 15) to gather preliminary data on the agent's pharmacokinetics (how the body processes the drug) and pharmacodynamics (how the drug works in the body).

Phase I trials are the first stage of testing in human subjects. Normally, a small (20-80) group of healthy volunteers will be selected. This phase includes trials designed to assess the safety (pharmacovigilance), tolerability, pharmacokinetics, and pharmacodynamics of a drug. These trials are often conducted in an inpatient clinic, where the subject can be observed by full-time staff. The subject who receives the drug is usually observed until several half-lives of the drug have passed. Phase I trials also normally include dose-ranging, also called dose escalation, studies so that the appropriate dose for therapeutic use can be found. The tested range of doses will usually be a fraction of the dose that causes harm in animal testing. Phase I trials most often include healthy volunteers.

Once the initial safety of the study drug has been confirmed in Phase I trials, Phase II trials are performed on larger groups (20-300) and are designed to assess how well the drug works, as well as to continue Phase I safety assessments in a larger group of volunteers and patients. When the development process for a new drug fails, this usually occurs during Phase II trials when the drug is discovered not to work as planned, or to have toxic effects.

Phase II studies are sometimes divided into Phase IIA and Phase IIB. Phase IIA is specifically designed to assess dosing requirements (how much drug should be given), whereas Phase IIB is specifically designed to study efficacy (how well the drug works at the prescribed dose(s)).

Some trials combine Phase I and Phase II, and test both efficacy and toxicity.

Phase III studies are randomized controlled multicenter trials on large patient groups (300–3,000 or more depending upon the disease/medical condition studied) and are aimed at being the definitive assessment of how effective the drug is, in comparison with current 'gold standard' treatment. Because of their size and comparatively long duration, Phase III trials are the most expensive, time-consuming and difficult trials to design and run, especially in therapies for chronic medical conditions.

It is common practice that certain Phase III trials will continue while the regulatory submission is pending at the appropriate regulatory agency. This allows patients to continue to receive possibly lifesaving drugs until the drug can be obtained by purchase. Other reasons for performing trials at this stage include attempts by the sponsor at "label expansion" (to show the drug works for additional types of patients/diseases beyond the original use for which the drug was approved for marketing), to obtain additional safety data, or to support marketing claims for the drug.

Once a drug has proved satisfactory after Phase III trials, the trial results are usually combined into a large document containing a comprehensive description of the methods and results of human and animal studies, manufacturing procedures, formulation details, and shelf life. This collection of information makes up the "regulatory submission" that is provided for review to the appropriate regulatory authorities in different countries. They will review the submission, and, it is hoped, give the sponsor approval to market the drug.

Phase IV trial is also known as Post Marketing Surveillance Trial. Phase IV trials involve the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it receives permission to be sold. Phase IV studies may be required by regulatory authorities or may be undertaken by the

sponsoring company for competitive (finding a new market for the drug) or other reasons (for example, the drug may not have been tested for interactions with other drugs, or on certain population groups such as pregnant women, who are unlikely to subject themselves to trials). The safety surveillance is designed to detect any rare or long-term adverse effects over a much larger patient population and longer time period than was possible during the Phase I-III clinical trials.

Reference: http://en.wikipedia.org/wiki/Clinical_trial

What is the Immunisation Advisory Centre (NZ)?

The Immunisation Advisory Centre (IMAC) is a nationwide organisation based at the School of Population Health at The University of Auckland.

Our aim is to provide New Zealanders with a local source of independent, factual information including benefits and risks regarding immunisation, and vaccine-preventable disease. The information we provide is based on international and New Zealand medical research and is supported by a large network of health professionals.

We provide a variety of products and services for consumers, health professionals, government agencies and the media to improve the understanding and quality of immunisation in New Zealand.

Website: www.immune.org.nz

What is the Immunisation Awareness Society (NZ)?

The Immunisation Awareness Society Inc. is a voluntary and charitable organisation founded in 1988 by Hilary Butler. Its members include parents, caregivers, other adults and a small minority of health professionals. The majority of IAS members have made the decision not to vaccinate themselves or their children. One of their objectives is to debate potential vaccination issues through symposiums, health forums, displays, talks, presentations and the media.

Website: www.ias.org.nz

Who is Judicial Watch (USA)?

“Judicial Watch has filed more than 150 lawsuits against federal, state, and local agencies and officials across the country seeking to promote transparency, integrity, and accountability in government and fidelity to the rule of law.”

Founder: Judicial Watch was founded in 1994 by conservative attorney Larry Klayman. In 2006 Klayman sued Judicial Watch and its president Tom Fitton charging financial and other mismanagement issues which damaged Judicial Watch, the donors and Klayman. The lawsuit is ongoing. Larry Klayman is now

the founder and chief representative of the Klayman Law Firm, which cites one of its areas of expertise as 'personal injury'.

President: Tom Fitton is the current president of Judicial Watch, a self-described "conservative, non-partisan, educational foundation," which, according to its mission statement, attempts to bring "transparency, accountability and integrity" to the federal government, primarily by filing lawsuits, FOIA requests, and other civil litigation and actions designed to generate public pressure on agencies and individuals within the federal government. Although Fitton asserts that he holds a B.A. in English, Klayman disputes that assertion and claims that Fitton admitted that he does not in fact have a Bachelor's degree. This dispute is one of the points of contention in a lawsuit brought against Fitton by Klayman in 2006 which is still in progress.

Funding: In 2002, Judicial Watch received \$1.1 million from The Carthage Foundation and a further \$400,000 from the Sarah Scaife Foundation. Both foundations are managed by Richard Mellon Scaife. The year before the Scaife Foundation gave \$1.35 million and Carthage \$500,000. Scaife is particularly well known for his financial support of conservative public policy organizations over the past two decades. Richard Mellon Scaife is a Pittsburgh billionaire who has financed numerous anti-Clinton activities and is known as the 'funding father of the right'.

Website: www.judicialwatch.org