

## QUADRIVALENT HPV VACCINE: Frequently Asked Questions

### Questions about vaccine efficacy and impact

Q1 If the vaccine is 90 to 100% effective, why do some trial results show only a small reduction in pre-cancerous lesions of the cervix?

Q2 I've read that infection with the HPV types in the vaccine is actually very rare. Is it?

Q3 How do we know that other HPV types won't replace those which we vaccinate against or even 'flourish'?

Q4 How do we know the vaccine will prevent cervical cancer when cancer takes years to develop and the trials ran for less than five years?

Q5 Aren't there easier steps to take to prevent cervical cancer like regular exercise and a healthy diet?

### Questions about vaccine safety

Q6 How do we know the vaccine is safe? I've read it was only tested in 1,700 young girls.

Q7 Does the vaccine cause fainting? I heard it made a lot of school girls very unwell.

Q8 How do we know the vaccine won't cause cancer? Surely if HPV can, a vaccine based on it might too?

Q9 Why wasn't the vaccine tested for genotoxicity and carcinogenicity, as stated in the product information?

Q10 I've heard the vaccine could cause infertility. Is this true?

Q11 Does the vaccine affect pregnancy outcomes?

Q12 Should I be concerned that this is a genetically engineered vaccine?

### Other issues

Q13 Is HPV vaccine compulsory, or is consideration being given to making it compulsory as discussed in the USA?

Q14 If all the trials were sponsored by the vaccine manufacturer, can we trust their data?

Q15 Why is there information on the Internet saying the vaccine is dangerous if it isn't?

Q16 Could receiving HPV vaccine make my daughter promiscuous?

## Questions about vaccine efficacy and impact

### Q1 If the vaccine is 90 to 100% effective, why do some trial results show only a small reduction in pre-cancerous lesions of the cervix?

The vaccine is highly effective at preventing type-specific HPV disease when given to women who are not already infected with those types. Because HPV trials have reported results for all women enrolled in the vaccine trials, including women infected before vaccination, and for all cervical disease regardless of type, the overall reduction in pre-cancerous lesions cited from these trials is low.

The quadrivalent HPV vaccine is 98% effective in preventing high grade cervical disease due to HPV types 16 and 18, in women who received all three doses of the vaccine and who were not infected with HPV type 16 or 18 prior to completion of the vaccination course.

Types 16 and 18 are found in 70–80% of cervical cancers, in 55% of high grade cervical lesions and in only 25% of low grade cervical lesions. Most low grade lesions do not progress on to cancer.\*

HPV vaccine works by stimulating the body to produce antibodies. These antibodies prevent infection with the four HPV types targeted by the vaccine (6, 11, 16 and 18), but they do not treat infection that is already there or prevent HPV infection due to other HPV types (about 40 types can infect the genital area).

HPV infection is very common (like the common cold) and very easily transmitted during sexual activity. Most people will be infected during their lives with one or more HPV types without ever knowing it. HPV infection rates are highest in young people; so, when a group of young women who are already sexually active are vaccinated, many will already have HPV infection. The vaccine will not prevent cervical disease in these women and will also not prevent infection and disease due to other types. This is why the overall effect of the vaccine in reducing cervical disease is limited when given to those who have already been sexually active.

The true impact of the vaccine is seen only when those women not infected with vaccine types before completion of the course of vaccination are examined for disease due to these types. In a recent publication in the *New England Journal of Medicine*, results of HPV vaccination with Gardasil® in over 12,000 women aged 15–26 years were reported. Analysis of the women who received all three doses, and who were not infected with HPV type 16 or 18 prior to completion of vaccination, showed that the vaccine was 98% effective in preventing high grade cervical disease due to types 16 and 18. However, if all women in the trial were included (including those who were already infected with HPV type 16 or 18 and who did not receive all vaccine doses), the vaccine was only 44% effective against all disease due to types 16 and 18 and 17% effective against all cervical disease. This analysis clearly demonstrates why the main target group for the vaccine is women prior to sexual activity (ie. young adolescents not infected with HPV) and also why Pap smears remain necessary (to find any pre-cancerous cervical changes due to existing HPV infection or new infections with non-vaccine high risk HPV types).

## Reference

*FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. New England Journal of Medicine 2007;356:1915-1927.*

**\*Further information:** HPV types 16 and 18 can be found in 70–80% of cervical cancers. This is because these types of HPV are the most likely of the many types that infect the cervix to persist long enough to disrupt the normal functioning of cells in the cervix and cause cancer. Types 16 and 18 are found in 55% of high grade cervical lesions (because there are more types that can persist long enough to cause these pre-cancerous changes) and a smaller proportion (25%) of low grade cervical lesions (because many HPV types can cause low grade lesions). Because HPV types 16 and 18 are responsible for a smaller proportion of pre-cancerous cervical lesions (those lesions picked up on a Pap smear) than cancers, the impact of the vaccine is relatively smaller in the prevention of Pap abnormalities than it is on cancers.

## References

- Clifford GM, Smith JS, Plummer M, Muñoz N, Franceschi S. Human papillomavirus types in invasive cervical cancer worldwide: a meta-analysis. *British Journal of Cancer* 2003;88:63-73.
- Clifford GM, Smith JS, Aguado T, Franceschi S. Comparison of HPV type distribution in high-grade cervical lesions and cervical cancer: a meta-analysis. *British Journal of Cancer* 2003;89:101-105.
- Clifford GM, Rana RK, Franceschi S, et al. Human papillomavirus genotype distribution in low-grade cervical lesions: comparison by geographic region and with cervical cancer. *Cancer Epidemiology, Biomarkers & Prevention* 2005;14:1157-1164.

## Q2 I've read that infection with the HPV types in the vaccine is actually very rare. Is it?

No, infection with at least one of the HPV types at some time in a person's life is very common. Studies in young women have found a very high risk of infection over time. Among women aged 14–20 years, 10–32% acquire HPV16 and 4–20% acquire HPV18 infection over a 2–4 year period. Studies that have measured antibody response to HPV in blood samples confirm that many people have been exposed to these viruses; for example, in a US population based study, 25% of women aged 20–29 years had been infected with HPV16. The true rate is likely to be higher as many people who become infected and clear the infection never make an antibody response. So while a recent US study found that, at a single point in time, few women had an active HPV infection with the HPV types covered by the HPV vaccine, this is like measuring how many people had chicken pox at one point in time and concluding that it must be rare. What is important is the likelihood of ever being infected which, as cited above, is substantial for sexually active women.

## References

- Brown DR, Shew ML, Qadadri B, et al. A longitudinal study of genital human papillomavirus infection in a cohort of closely followed adolescent women. *Journal of Infectious Diseases* 2005;191:182-192.
- Dunne EF, Unger ER, Sternberg M, et al. Prevalence of HPV infection among females in the United States. *JAMA* 2007;297:813-819.
- Stone KM, Karem KL, Sternberg MR, et al. Seroprevalence of human papillomavirus type 16 infection in the United States. *Journal of Infectious Diseases* 2002;186:1396-1402.
- Winer RL, Lee SK, Hughes JP, et al. Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students. [erratum appears in *Am J Epidemiol.* 2003 May 1;157(9):858]. *American Journal of Epidemiology* 7:218-226
- Woodman CB, Collins S, Winter H, et al. Natural history of cervical human papilloma-virus infection in young women: a longitudinal cohort study. *Lancet* 2001;357:1831-1836.

### Q3 How do we know that other HPV types won't replace those which we vaccinate against or even 'flourish'?

Virological studies of HPV indicate that there is very little, if any, interaction between virus types, ie. they don't compete with each other. Therefore, it is unlikely that other viruses will replace the cancer-causing types 16 and 18 if infection with those types is prevented through vaccination.

Current genetic and evolutionary understanding of HPV is reassuring in supporting the relative ecological stability of HPV over long term periods. HPV16 appears to be unique in terms of its proclivity to cause disease. So it is viewed as unlikely that there will be competitive adaptation of other HPV types to fill the 'ecological niche' left by removal of HPV types 16 and 18. However, this certainly does require monitoring and, in order to measure the reduction in infection with types targeted by vaccination, a surveillance system to monitor the types of HPV infection over time in Australia is being investigated.

Although it is unlikely that there will be replacement disease following the prevention of HPV type 16 and 18 infection, we will still see disease from the remainder of the 40 or so genital HPV types that cause 75% of the low grade cervical lesions and the 13 other high risk types that cause 45% of high grade disease.

#### References

Bernard HU. *The clinical importance of the nomenclature, evolution and taxonomy of human papillomaviruses. Journal of Clinical Virology* 2005;32(Suppl 1):S1-S6.

Bernard HU, Calleja-Macias IE, Dunn ST. *Genome variation of human papillomavirus types: phylogenetic and medical implications. International Journal of Cancer* 2006;118:1071-1076.

Chan SY, Delius H, Halpern AL, Bernard HU. *Analysis of genomic sequences of 95 papillomavirus types: uniting typing, phylogeny, and taxonomy. Journal of Virology* 1995;69:3074-3083.

Halpern AL. *Comparison of papillomavirus and immunodeficiency virus evolutionary patterns in the context of a papillomavirus vaccine. Journal of Clinical Virology* 2000;19:43-56.

Lowndes CM. *Vaccines for cervical cancer. Epidemiology & Infection* 2006;134:1-12.

### Q4 How do we know the vaccine will prevent cervical cancer when cancer takes years to develop and the trials ran for less than five years?

Research has demonstrated that HPV is a necessary cause of cervical cancer. While most HPV infections are cleared by the body and never result in cancer, if the infection persists the virus can eventually integrate into cells and prevent the cell from repairing itself normally. Over time, cancer can result. While other factors may be important in determining whether HPV infection persists and progresses to cancer (see Q5 below), cancer does not occur without HPV infection.

Research has also provided a better understanding of the link between HPV infection and the various cell changes that occur in the cervix following infection.

Because it is unethical to allow cancer to develop, and because of the time involved, the vaccine trials used other outcomes along the pathway from HPV infection to cancer to determine whether the vaccine will prevent cancer.

Firstly, the vaccines have been shown to prevent persistent infection, which is a necessary initial step on the pathway to cervical cancer. More importantly the vaccines have been shown to prevent pre-cancerous disease of the cervix caused by HPV types 16 and 18, which is a step closer to cancer itself. This outcome is taken as the most

practical measure of the success of vaccination in much the same way that it is accepted that detection and removal of these lesions through Pap screening programs reduces cervical cancer.

**Further information:** In 2003, a World Health Organization (WHO) consultation group developed recommendations for appropriate measures of HPV vaccine efficacy (Pagliusi 2004). Cervical cancer is not a feasible stand alone endpoint due both to ethical considerations and the fact that very large trials would need to be ongoing for at least 20 years to accrue enough cases. The consultation generally agreed that CIN2/3 (cervical intra-epithelial neoplasia grade 2 and 3), as well as cancer, should be the globally defined endpoint for population-based vaccine efficacy studies. The WHO consultation considered that the virological endpoint of persistent HPV infection was also a useful endpoint for vaccine studies.

The four key features of (type-specific) CIN2/3/AIS (adenocarcinoma in situ) (FIGO Stage 0 cervical cancer) that make them appropriate endpoints for determining vaccine efficacy are that:

- they are obligate precursors of cervical cancer;
- they are closely associated in temporal sequence to the development of invasive cervical cancer;
- they are associated with a high risk of development of invasive cervical cancer; and
- reductions in incidence or treatment are shown to result in a reduction in risk of invasive cervical cancer.

#### Reference

Pagliusi SR, Aguado MT. Efficacy and other milestones for human papillomavirus vaccine introduction. *Vaccine* 2004;23:569-578.

#### Q5 Aren't there easier steps to take to prevent cervical cancer like regular exercise and a healthy diet?

It is not possible for a sexually active person to guarantee that they will never be infected with HPV and, if infected, to guarantee that their body's immune system will be able to clear the virus. The only way to ensure protection from infection is to remain sexually abstinent. This is why, either with or without vaccination, all women who have ever been sexually active should have Pap smears every two years.

While there is evidence that a healthy diet and exercise can help protect against certain other cancers, such as bowel cancer, there is no definitive evidence that these factors will protect against cervical cancer. There is some evidence suggesting anti-oxidant nutrients may play a protective role but this remains to be confirmed.

Whether a woman is at risk of being unable to clear an HPV infection, and thus of developing cervical cancer, appears to be determined by:

- genetic factors;
- whether the woman smokes;
- whether there is co-infection with other sexually transmitted infections, such as herpes or chlamydia;
- whether there is severe immunosuppression, such as HIV infection.

Other proven risk factors for cervical cancer include having had a very large number of births and long term oral contraceptive use.

A woman may be able to reduce her risk of HPV infection somewhat by consistent condom use, but it should be emphasised that HPV can be transferred via genital skin that is not covered by the condom. Smokers have a higher risk of persistent HPV infection and cervical cancer than non-smokers and quitting smoking can reduce the risk of persistent HPV infection.

### References

Ahdieh L, Muñoz A, Vlahov D, et al. Cervical neoplasia and repeated positivity of human papillomavirus infection in human immunodeficiency virus-seropositive and -seronegative women. *American Journal of Epidemiology* 2000;151:1148-1157.

Bosch FX, Lorincz A, Muñoz N, Meijer CJ, Shah KV. The causal relation between human papillomavirus and cervical cancer. *Journal of Clinical Pathology* 2002;55:244-265.

Green J, Berrington de Gonzalez A, Sweetland S, et al. Risk factors for adenocarcinoma and squamous cell carcinoma of the cervix in women aged 20-44 years: the UK National Case-Control Study of Cervical Cancer. *British Journal of Cancer* 2003;89:2078-2086.

Hildesheim A, Wang SS. Host and viral genetics and risk of cervical cancer: a review. *Virus Research* 2002;89:229-240.

International Collaboration of Epidemiological Studies of Cervical Cancer (ICESCC). Carcinoma of the cervix and tobacco smoking: collaborative reanalysis of individual data on 13,541 women with carcinoma of the cervix and 23,017 women without carcinoma of the cervix from 23 epidemiological studies. *International Journal of Cancer* 2006;118:1481-1495.

International Collaboration of Epidemiological Studies of Cervical Cancer (ICESCC). Cervical carcinoma and reproductive factors: collaborative reanalysis of individual data on 16,563 women with cervical carcinoma and 33,542 women without cervical carcinoma from 25 epidemiological studies. *International Journal of Cancer* 2006;119:1108-1124.

Madeleine MM, Brumback B, Cushing-Haugen KL, et al. Human leukocyte antigen class II and cervical cancer risk: a population-based study. *Journal of Infectious Diseases* 2002;186:1565-1574.

Muñoz N, Castellsagué X, de González AB, Gissmann L. Chapter 1: HPV in the etiology of human cancer. *Vaccine* 2006;24(Suppl 3):S1-S10.

National Health and Medical Research Council (NHMRC). Screening to prevent cervical cancer: guidelines for the management of asymptomatic women with screen detected abnormalities. Canberra: NHMRC; 2005. Available at: <http://www.nhmrc.gov.au/publications/synopses/files/wh39.pdf> (accessed Aug 2007).

## Questions about vaccine safety

### Q6 How do we know the vaccine is safe? I've read it was only tested in 1,700 young girls.

All of the available data to date, both in the vaccine trials, in which over 27,000 people received the vaccine, and in clinical usage, indicate that the vaccine is safe. The vaccine has been evaluated for safety and efficacy by the Food and Drug Administration (FDA) in the USA, the Therapeutic Goods Administration (TGA) in Australia and the European Medicines Agency (EMA), all of which have concluded that the vaccine is safe and effective.

Vaccines require clinical testing in greater numbers than most other clinical drugs in order to meet regulatory conditions for approval. HPV vaccine trials for Gardasil® involved over 27,000 people worldwide as at April 2006. Safety information was collected on over 13,000 individuals who received HPV vaccine. In addition, over 5 million doses have been distributed in the US and over 22 million doses distributed in Australia to date. The other HPV vaccine, Cervarix®, has been tested in similar numbers. These studies were large enough to detect adverse reactions occurring as infrequently as one in several thousand.

Two specific studies evaluated the safety and immunogenicity of the vaccine in males and females aged 9 to 15 years. One study involved 1,700 people aged 9 to 15 years, of whom about 1,100 received the vaccine. Another study, which included Australian subjects, enrolled more than 1,000 males and females aged 10 to 15 years, all of whom received the HPV vaccine. The vaccine was well tolerated in these studies and young people produced antibody responses at least twice those of older women, in whom the vaccine has been demonstrated to provide protection against HPV. The vaccines have not been tested for their effectiveness at preventing Pap abnormalities and HPV infection in young girls due to the undesirability of collecting invasive genital specimens in young girls. Young females who were vaccinated before the age of 16 are now being followed up to confirm the vaccines' effectiveness as these women become sexually active.

The main side effect of the vaccines is local reactions at the injection site (pain, redness and swelling) which occur in about 80% of those who receive the vaccine. The most common symptoms reported in the seven days following vaccination with Gardasil® are fever (slightly more frequently than in those who received a placebo injection), and headache and fatigue, but these are no more common than in placebo recipients.

There were very few serious adverse events reported following vaccination (<0.1%) and they were no more frequent than in those receiving placebo. In the clinical studies, subjects were evaluated for new medical conditions, including autoimmune diseases, occurring in up to four years of follow-up. No trends, patterns of new medical conditions or safety concerns were identified during the follow-up period.

The most important contraindication to vaccination with Gardasil® is known anaphylaxis (severe allergy) to yeast or severe allergy to any other vaccine ingredient(s). As with any medication, there is always a small risk of an allergic reaction (anaphylaxis) following administration.

In-depth analysis of women vaccinated in these trials is continuing and, in particular, 5,500 women in Scandinavia are being followed by linkage to cancer, Pap and other health registers to monitor the duration of vaccine effectiveness and to confirm its safety.

The US Vaccine Adverse Events Reporting System (VAERS) collects reports of any problems following vaccination. These reports do not establish any causal link between the vaccine and the problem, as many health problems arise in the population every day even in the absence of vaccination, but provide a system for detecting any signals of concern, such as more reports of a given problem than would be expected. If such a signal is detected, special studies are designed to establish whether the problem is related to vaccination.

In Australia, reports of problems following vaccination are reported to the Therapeutic Goods Administration (TGA) and reviewed by experts. In December 2007, the TGA reported on initial adverse events reports following HPV vaccine (<http://www.tga.gov.au/alerts/medicines/gardasil.htm>). The report documents the occurrence of allergy and anaphylaxis after vaccination. While these events are rare, all patients should be observed for 15 minutes after vaccination.

### References

Block SL, Nolan T, Sattler C, 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;118:2135-2145.

Markowitz LE, Dunne EF, Saraiya M, et al. Quadrivalent human papillomavirus vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morbidity and Mortality Weekly Report* 2007;56(RR-2):1-24.

Reisinger KS, Block SL, Lazcano-Ponce E, et al. Safety and persistent immunogenicity of a quadrivalent human papillomavirus types 6, 11, 16, 18 L1 virus-like particle vaccine in preadolescents and adolescents: a randomized controlled trial. *Pediatric Infectious Disease Journal* 2007;26:201-209.

### Q7 Does the vaccine cause fainting? I heard it made a lot of school girls very unwell.

Some people who receive an injection of any kind do faint or have other symptoms associated with fainting (called syncope or a vasovagal attack) such as headache, and feeling weak, nauseous and/or dizzy. Others may become very anxious due to fear of needles or, in situations where many people are being vaccinated, such as at school, due to the responses of those around them. These reactions are more common in adolescents and young people. Such symptoms are certainly distressing but resolve with simple treatment such as lying down, adequate food and drink intake and reassurance. When administering the vaccine, make sure patients have eaten properly before vaccination and are observed for 15 minutes afterwards.

All such episodes occurring in the school setting are reported and investigated as appropriate. There is no evidence that there is anything about the HPV vaccine that causes fainting more than other injections.

In May 2007, media reports publicised that a group of school girls in Melbourne became unwell after being vaccinated. All of these episodes fully resolved and were attributed by the treating medical staff to fainting and anxiety/stress reactions. The batch of HPV vaccine was fully investigated and found to be a normal batch.

### References

Clements CJ. Gardasil™ and mass psychogenic illness [letter]. *Australian & New Zealand Journal of Public Health* 2007;31:387.

Markowitz LE, Dunne EF, Saraiya M, et al. Quadrivalent human papillomavirus vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morbidity and Mortality Weekly Report* 2007;56(RR-2):1-24.

## Q8 How do we know the vaccine won't cause cancer? Surely if HPV can, a vaccine based on it might too?

No, the HPV vaccine does not contain any of the viral proteins which cause cancer. The pathways by which these viral proteins can disrupt normal cell growth and repair mechanisms, to ultimately result in cancer, are well described in the scientific literature.

HPV vaccine is made using recombinant DNA technology and contains only 'virus-like particles'. The vaccine is made up of outer coat proteins of the virus only, with no viral DNA. It is not a live virus or a killed virus, and is not infectious.

### References

- Burd EM. Human papillomavirus and cervical cancer. *Clinical Microbiology Reviews* 2003;16:1-17.
- Garland SM. Human papillomavirus update with a particular focus on cervical disease. *Pathology* 2002;34:213-224.
- Greenblatt RJ. Human papillomaviruses: diseases, diagnosis, and a possible vaccine. *Clinical Microbiology Newsletter* 2005;27:139-145.
- Münger K, Howley PM. Human papillomavirus immortalization and transformation functions. *Virus Research* 2002;89:213-228.
- Villa LL, Bernard HU, Kast M, et al. Past, present, and future of HPV research: highlights from the 19th International Papillomavirus Conference-HPV2001. *Virus Research* 2002;89:163-173.
- Wentzensen N, Vinokurova S, von Knebel Doeberitz M. Systematic review of genomic integration sites of human papillomavirus genomes in epithelial dysplasia and invasive cancer of the female lower genital tract. *Cancer Research* 2004;64:3878-3884.

## Q9 Why wasn't the vaccine tested for genotoxicity and carcinogenicity, as stated in the product information?

These tests are only performed when there is a plausible mechanism or concern regarding genotoxicity or carcinogenicity. Most vaccines are not tested for genotoxicity or carcinogenicity. This is consistent with WHO guidelines (2003) which state:

*"Genotoxicity studies are normally not needed for the final vaccine formulation. However, they may be required for particular vaccine components such as novel adjuvants and additives. Carcinogenicity studies are not required for vaccine antigens."*

The Therapeutic Goods Administration (TGA) in Australia adopts the guidelines of the European Medicines Agency (EMA). In relation to vaccine assessment, these state "Genotoxicity and carcinogenicity studies are normally not needed" and recommend that novel synthetic vaccine adjuvants require genotoxicity testing but not carcinogenicity testing.

### References

- Human Medicines Evaluation Unit, The European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products (CPMP). Note for guidance on preclinical pharmacological and toxicological testing of vaccines (CPMP/SWP/465/95). 1997. Available at: <http://www.emea.europa.eu/pdfs/human/swp/046595en.pdf> (accessed Aug 2007).
- The European Medicines Agency Evaluation of Medicines for Human Use, Committee for Medicinal Products for Human Use (CHMP). Guideline on adjuvants in vaccines for human use (EMA/CHMP/VEG/134716/2004). 2005. Available at: <http://www.emea.europa.eu/pdfs/human/vwp/13471604en.pdf> (accessed Aug 2007).
- World Health Organization (WHO). WHO guidelines on nonclinical evaluation of vaccines. 2003. Available at: [http://www.pasteur.fr/recherche/Crvbm/Documents/WHO\\_Nonclinical\\_evaluation\\_vaccines\\_Nov\\_2003.pdf](http://www.pasteur.fr/recherche/Crvbm/Documents/WHO_Nonclinical_evaluation_vaccines_Nov_2003.pdf) (accessed Aug 2007).

## Q10 I've heard the vaccine could cause infertility. Is this true?

No. There is no biologically plausible way in which the vaccine could cause infertility. HPV infection, unlike some other sexually transmitted infections such as chlamydia, is not a cause of infertility. Studies of high doses of the vaccine in female rats showed no effect on fertility.

Some Internet sites report disturbing claims that one ingredient of the vaccine, polysorbate 80, causes infertility in rats. This is based on one study of newborn rats (10–17g size) injected intraperitoneally with very large doses (20 to 200 times the amount in Gardasil®). However, the Therapeutic Goods Administration has reviewed available data regarding polysorbate 80 and fertility and concluded that there is no evidence that polysorbate 80 at a level of 50 µg per 0.5mL dose in Gardasil® poses a hazard to human reproduction or fertility. Polysorbate 80 is found in numerous medications, including other vaccines, and is used as a food additive and in cosmetics. It is listed in “Substances that may be used in listed medicines in Australia” (TGA April 2007 <http://www.tga.gov.au/cm/listsubs.pdf>) and as a food additive (emulsifier code 433) by Food Standards Australia New Zealand.

**Further information:** Concerns about fertility and pregnancy outcomes are a reasonable concern given that this vaccine is targeted at young women. However, providers and the public should be aware that scares about vaccines leading to infertility are a common tactic used by anti-vaccination campaigners seeking to disrupt immunisation campaigns. For example, scare campaigns in Nigeria in 2003 about the polio vaccine leading to infertility resulted in reduced vaccine uptake and consequent polio outbreaks.

### References

Centers for Disease Control and Prevention (CDC). *Resurgence of wild poliovirus type 1 transmission and consequences of importation - 21 countries, 2002-2005. MMWR Morbidity and Mortality Weekly Report 2006;55:145-150.*

Raufu A. *Nigeria postpones programme of polio immunisation. BMJ 2004;328:1278.*

## Q11 Does the vaccine affect pregnancy outcomes?

While it is recommended that vaccination be avoided during pregnancy, there is no indication that inadvertent administration of the vaccine to a pregnant woman will result in an increased risk of adverse pregnancy outcomes. Although participants were requested to avoid pregnancy, during Phase 3 trials of Gardasil® there were 1,244 pregnancies in women who received Gardasil® and 1,272 pregnancies in placebo recipients. The rate of adverse pregnancy outcomes was similar in vaccine and placebo recipients. In particular, there was no evidence of an impact on spontaneous abortion rates, late foetal deaths or number of live births. Congenital anomalies were rare and the types of anomalies that occurred in both groups were consistent with those generally observed in pregnancies in women in the 16–26 year age group.

Women who wish to conceive following a course of Gardasil® vaccine are able to commence trying to fall pregnant immediately following the third dose, as the vaccine is not a live virus.

For women who fall pregnant before completing the three dose vaccine schedule, the schedule can safely be resumed following pregnancy. As with other vaccines, there is no need to recommence the vaccine schedule from the first dose but recommence with the due dose (second or third).

## Q12 Should I be concerned that this is a genetically engineered vaccine?

No, this vaccine does not contain DNA and cannot 'interact' with your DNA. The genetic engineering of this vaccine means it contains very pure protein rather than killed or live viruses. HPV vaccine is made using recombinant DNA technology. Hepatitis B vaccine is made using similar technology.

The technique, of being able to produce the protein found in the coat of the virus, which then naturally self-assembles into 'virus-like particles' (VLPs), was first discovered by Professor Ian Frazer and colleagues in Brisbane. Prior to this discovery, all attempts to create a vaccine against HPV had proven unsuccessful. The genetic code (or instructions) to make the protein of the viral coat is inserted into either a yeast (for Gardasil<sup>®</sup>) or insect cell (for Cervarix<sup>®</sup>). The yeast or insect cell then makes the protein which assembles itself into VLPs which have the same shape (a sphere) as HPV but contain no viral DNA.

### Reference

Zhou J, Sun XY, Stenzel DJ, Frazer IH. Expression of vaccinia recombinant HPV 16 L1 and L2 ORF proteins in epithelial cells is sufficient for assembly of HPV virion-like particles. *Virology* 1991;185:251-257.

## Other issues

### Q13 Is HPV vaccine compulsory, or is consideration being given to making it compulsory as discussed in the USA?

No. Routine vaccinations are not compulsory in Australia. Vaccination is an individual choice and each person should consider the risks and benefits for themselves, in consultation with their immunisation provider. Vaccination is widely accepted in Australia, with rates of vaccination in babies of over 94%, and is responsible for a reduction in morbidity and mortality from many diseases.

#### Reference

*Brotherton J, Wang H, Schaffer A, et al. Vaccine preventable diseases and vaccination coverage in Australia, 2003 to 2005. Communicable Diseases Intelligence 2007;31(Suppl):viii-S152.*

### Q14 If all the trials were sponsored by the vaccine manufacturer, can we trust their data?

There are many processes in place to ensure the integrity of the data presented by manufacturers of vaccines.

Regulatory requirements for vaccines are stringent. Prior to undertaking the HPV vaccine trials, large regulatory agencies such as the Food and Drug Administration (FDA) in the US were consulted by the manufacturers to ensure that all relevant efficacy and safety outcomes of interest would be measured and that the trials would be large enough to demonstrate the outcomes with sufficient statistical certainty to allow registration of the product should the trials prove successful.

Clinical trials are all registered on a publicly accessible register of clinical trials. This ensures that results of trials cannot be 'buried' and that negative as well as positive results are apparent.

All trials have to meet ethical approvals by independent ethics committees of participating institutions. Trials are conducted by academic research organisations, rather than by the sponsor company themselves. The trials were conducted in a blinded, randomised fashion which means that neither the participant nor the doctor/study personnel knew who had received the active vaccine. This was to reduce any possible bias in the reporting and analysis of effects of the vaccine. Trials are overseen by independent safety panels who are blinded to which participants are receiving which treatment.

Trial results submitted to scientific journals for publication are subject to 'peer review'. This means that the results are independently scrutinised by experts in the field prior to publication.

Before licensure of vaccines, regulatory authorities request specific data from the manufacturers and conduct their own analyses of the trial data. Data are subject to independent scrutiny.

In Australia, the Therapeutic Goods Administration considers data about the vaccine with standard requirements and evaluates the safety and efficacy of the vaccine in detail before recommending that it be registered for use.

The Australian Technical Advisory Group on Immunisation (ATAGI) provides independent expert advice to government regarding the potential role of the vaccine in Australia after considering the data on the vaccine as well as information on the disease to be prevented in the Australian setting. The Pharmaceutical Benefits Advisory Committee (PBAC) considers submissions from the vaccine manufacturers, who must demonstrate that the use of the vaccine would be cost-effective compared to the current situation, in order to qualify for subsidy at a negotiated price to government. PBAC also receives advice from ATAGI.

### Q15 Why is there information on the Internet saying the vaccine is dangerous if it isn't?

There are many competing interests and a wide range of views available on the Internet and it is often difficult to determine whose opinion it is that you are reading.

Some people who choose alternative lifestyles may reject mainstream medicine including vaccinations. While this position should be respected as their choice, it is important for others who are considering vaccination to be aware that some information provided on the Internet comes from organisations or people who are philosophically completely opposed to vaccination.

Anti-vaccination groups voice concern about most vaccines and this now includes HPV vaccines. Their perceptions can be found at websites such as those of the Australian Vaccination Network (AVN) and the National Vaccination Information Center (NVIC). Press releases from such organisations may often be alarming and controversial and thus generate considerable media interest.

### Q16 Could receiving HPV vaccine make my daughter promiscuous?

No, there is no evidence that receiving HPV vaccine could lead to promiscuity. The assumptions underlying such a suggestion (that perceptions of HPV risk prevent adolescents engaging in risky sexual behaviour and that fear of HPV is a motivation for abstinence/safe sex) are not supported by evidence. A US study found that only 7% of women cited fear of sexually transmitted diseases as a main reason for not having sex.

In the participants in the HPV vaccine trials there was no increase in number of sexual partners following vaccination. Initiation of sexual activity is influenced by many other factors such as individual psychological factors, drug and alcohol use, family communication and support, community relationships, school factors and perceptions of peer sexual activity. There is good evidence that receiving information about sexually transmitted infections, providing condoms or discussing sex *does not* result in earlier or more sexual activity.

### References

Liddon N. *Behavioural issues related to HPV vaccination. Summary of presentation to Advisory Committee on Immunization Practices (ACIP), February 2006. Available at: <http://www.cdc.gov/vaccines/recs/acip/downloads/min-feb06.pdf> (accessed Aug 2007).*

Monk BJ, Wiley DJ. *Will widespread human papillomavirus prophylactic vaccination change sexual practices of adolescent and young adult women in America? Obstetrics & Gynecology 2006;108:420-424.*