

The Facts about Human Papillomavirus (HPV), Cervical Cancer

And HPV Vaccine

- HPV 16/18 is a common infection in most women (80% of women will be infected with HPV at some time) but in 90% of cases it is harmless. Most HPV infections do not progress to warts or cervical cancer ^{1, 2, 3}
- It is also known that HPV infection on its own is not sufficient to cause cervical cancer ^{1, 3, 4}.
- The Australian Health Department refers to this vaccine as an HPV vaccine not as a cervical cancer vaccine ⁵. This is because in 2007 when it was marketed to women it had not been demonstrated to prevent any case or death from cervical cancer ⁶.
- In 2011 Professor Ian Frazer (the scientist who developed the vaccine) stated that 'HPV vaccine *may prevent* cervical cancer' ⁷. This was 6 years after it was promoted to women to prevent cervical cancer. In this newspaper article (2011) it is stated that 'as cervical cancer takes many years to develop further work must be conducted to confirm that the vaccine prevents the (cervical) cancer' ⁷
- Whilst HPV infection with 1 of 20 HPV genotypes is necessary for cancer development *it does not cause cancer on its own*. The presence of a co-factor is necessary to progress an HPV infection to carcinoma ^{1, 2, 3, 4, 8}
- Several co-factors have been identified as necessary for the progression of normal epithelial cells to cancer. Some of the co-factors that have been identified are ^{1, 3, 4}:
 - a) multiple partners for the male or female
 - b) a high number of births (parity)
 - c) the presence of HPV infection plus another virus (for example HPV + Herpes Simplex Virus Type 2)
 - d) prostitution
 - e) sex without a condom/microbicides

- f) low socioeconomic status (poor hygiene/sanitation/nutrition conducive to sexually transmitted diseases)
 - g) immunosuppression
 - h) smoking
 - i) oral contraceptives
- If the co-factors are not present HPV infection does not progress to cancer ^{3, 8}
 - Four out of five women who get cervical cancer live in developing countries not *developed countries such as Australia, Europe and the USA* ^{1, 9}
 - Australia has the second lowest incidence of cervical cancer in the world (among countries with comparable cancer registration) and Pap screening is almost 100% effective in detecting and preventing deaths from cervical cancer (GLOBOCAN 2002 in ³).
 - In 2002, before the vaccine was introduced, the death rate from cervical cancer in Australia was 1.7/100,000 women and the incidence rate was 6.9/100,000 women ^{3, 9}. This represents a very low risk to Australian women prior to the vaccine being introduced.
 - In 2007, when this vaccine was first promoted as a ‘cervical cancer vaccine’, the public was not informed of the low risk that cervical cancer presented to Australian women. Prof Ian Frazer (the creator of the vaccine) was named ‘Australian of the Year’ in 2006 for ‘developing a vaccine to prevent and treat cervical cancer’ ¹⁰.
 - In developed countries (e.g. Australia, USA, Europe) cervical cancer accounts for 3.6% of new cancers and in the developing world it accounts for 83% of new cancers ⁹.
 - The cumulative lifetime risk of developing cervical cancer in *developed* nations is 0.8% and of dying of cc is 0.25% ⁹
 - The prevalence of HPV 16/18 is similar in all countries but the incidence of cervical cancer is significantly higher in developing countries ¹¹. Australia’s indigenous women

have 5 times the risk of dying from cervical cancer than non-indigenous women ¹². This indicates that lifestyle and environmental factors play a role in progressing HPV infection to cervical cancer ¹².

- There are at least 20 strains of HPV that are associated with causing cancer and 15 of these are classified as ‘high-risk’ meaning they are more likely to persist ¹. The HPV vaccine only covers 2 of the 20 HPV genotypes that are associated with cancer ¹³.
- Women will still need Pap screening because the vaccine does not protect against all cancer causing HPV types ¹².
- Gardasil vaccine has not been demonstrated to be safer or more effective than Pap screening combined with loop electrosurgical excision procedure (LEEP): the procedure used to remove CIN 2 and 3 lesions. Nor can it improve the diagnosis of serious cervical cancer outcomes ¹⁴.
- Infection with Human Papillomavirus (HPV) 16/18 (the strains covered in the vaccine) rarely progress to cervical cancer ^{1, 2, 3}

The HPV Vaccine Trials:

- In 2003 Merck & Co did not trial this vaccine against cervical cancer. It was trialled for 3-4 years in women 16 – 26 years of age against *pre-cancerous lesions* ⁸. This was used as a surrogate for cervical cancer even though most pre-cancerous lesions in young women *do not lead to cancer* ^{3, 14, 15}
- The majority of high-grade lesions (CIN 2 and 3) in young women 16-26 years of age regress naturally and without treatment ^(3, 14, 15) and this end-point was used as a surrogate to determine vaccine efficacy in the clinical trials ¹³.
- In 2006 Gardasil® was named the pharmaceutical “Brand of the Year” by the magazine *Pharmaceutical Executive* for building a ‘market out of thin air’ ¹⁶. The trials for this drug did not observe that it would prevent any cervical cancer ⁶

- In the clinical trials researchers were observing the incidence of high-grade pre-cancerous lesions in 16-26 year old women. In young women high-grade pre-cancerous lesions (CIN 2 and 3) are common and they are often misdiagnosed (14, 15). They also have a high clearance rate: most do not lead to cancer later in life 3, 14, 15.
- Whilst the vaccine will prevent infection from 2 strains of 20 cancer causing HPV genotypes it is still undetermined in 2013 how this will affect the incidence and mortality of cervical cancer that is associated with 20 HPV genotypes 17.
- CSL (pharmaceutical company) funded the research for the development of this vaccine at the University of Queensland 18
- Clinical trials for the vaccine were funded by Merck (manufacturer of the vaccine) (13) and the study was designed, managed, and analysed by Merck in conjunction with external academics 6.

The conflicts of interest of the academics include:

1. Indiana University declared that Merck had signed a confidential agreement that pays the university on the basis of certain landmarks regarding HPV vaccine 6
2. 10 authors of the clinical trials were current or former employees of Merck and 18 other authors, including Bosch, Villa and Munoz (the researchers who claimed HPV 16/18 are the determining and independent cause of cervical cancer) reported receiving consulting fees and having served on paid advisory boards for Merck 6.
3. Some trial investigators had also received consulting fees and served on the advisory board for GlaxoSmithKline (GSK) 6
4. Dr. Bosch had received consulting fees and served on the advisory board for GSK and Digene and he had also received lecture fees from Merck and GSK. Research grants were also provided to him from Merck and GSK through his institution to fund the vaccine trials and the epidemiological studies 6.
5. 11 of the authors including Villa and Munoz received lecture fees from Merck, Sanofi-Pasteur, and Merck Sharp and Dohme 6
6. Dr. Brown and Dr. Skjeldestad received funding from Merck for natural history studies of HPV infection. Dr. Myers received funding from Merck for conducting modelling studies of the effectiveness and cost-effectiveness of the vaccine in different settings.

7. 17 authors received funding from Merck through their institutions to conduct clinical trials of the vaccine ⁶
- In 2005 CSL also entered into a cross-licensing agreement with GlaxoSmithKline, the pharmaceutical company producing the competitor HPV vaccine: Cervarix ¹⁹
 - From 2003 – 2007 Gardasil was tested for efficacy against pre-cancerous lesions but safety data comparing vaccinated and unvaccinated groups was not collected for this time period ¹³. There are no long-term studies (1-3 years) of all the health outcomes from the use of Gardasil.
 - Cervical Cancer takes 8 - 25 years to develop and most pre-cancerous lesions in young women are not an indicator of cancer later in life ³. This surrogate was an inadequate indicator for determining the efficacy of HPV vaccine against cancer.

Safety Concerns

- Gardasil was licensed in 2006 and up to September 2012 there were 21,265 adverse events (AE's) reported to the US CDC and FDA alone ¹⁴. Globally there have been many more AE's associated with HPV vaccines. The US CDC data includes 78 deaths, 363 life-threatening events, 609 permanently disabled, 2,000 cases listed as serious or prolonged hospitalisation and 9,565 requiring an emergency room visit ¹⁴.
- This is only a proportion of the AE's because the US CDC monitoring system and Australia's TGA monitoring system are *passive* surveillance systems ²⁴. This means they rely on voluntary reporting of temporal events *only*. As vaccine ingredients can cause delayed adverse events the only type of system that would be able to establish causal relationships with adverse events is an *active* surveillance system: one that follows the health outcomes for every vaccinated individual for a minimum of 1 year.
- The CDC and the TGA admit that the surveillance systems cannot establish causal relationships between the vaccine and the adverse events. This allows the government to claim that the adverse events are a 'coincidence'. This is not a scientific evidence-based policy.
- It is known that passive reporting systems will only represent about one-tenth of the possible adverse events that actually occur ²⁰. Any delayed reactions will not be reported.

- Despite the voluntary reporting of adverse events Gardasil has been responsible for 61% of all serious AE's compared to all other vaccines in the US vaccination schedule (including 63.8% of all deaths and 81.2% of all cases of permanent disability) in females younger than 30 years of age ¹⁴.
- HPV vaccine contains genetically modified DNA ¹³
- Gardasil contains 225 micrograms of aluminium adjuvant (225 ug amorphous aluminium hydroxyphosphate sulphate). Many times more than most vaccines and this adjuvant is known to cause allergies/anaphylaxis and autoimmune reactions in humans ²⁰
- The trials did not use a true placebo to test the safety of the vaccine. The manufacturer funded clinical trials used the adjuvant, aluminium hydroxyphosphate sulphate (classified as a neuro-immunotoxic substance) as the placebo in the unvaccinated group and this substance does not allow the researchers to accurately compare the adverse health outcomes that might occur from the vaccine with a group that is completely unvaccinated..
- For example, in the pre-licensure clinical trial for Gardasil there were 245 serious reactions (indicative of an autoimmune disease) from the 'vaccine' group and 218 from the 'aluminium hydroxyphosphate sulphate' group. How would these figures compare to a group with no vaccine or aluminium adjuvant? This is a flaw in the experimental design of the trial ²².
- Other ingredients of the vaccine include: sodium borate (borax), polysorbate 80, L-histidine hydrochloride, 4 recombinant VLP's: HPV types – 16, 18, 11 and 6, amino Acids, carbohydrates, mineral salts, vitamins ¹³
- There are an unusually high number of AE's associated with HPV vaccines with nervous-system-related disorders ranking the highest in frequency ¹⁴. When the global reports of adverse events are pooled for Gardasil the data suggests that the risks of HPV vaccination have not been fully evaluated in the pre-licensure trials ¹⁴.
- Yet the US CDC and the Australian TGA are evaluating selective data (not the global safety data) and they are concluding that 'HPV vaccines are safe and effective'.
- The many known side-effects from HPV vaccines include death and life-long neurodegenerative/autoimmune disorders. These are documented in the pre-licensure clinical trials and at www.sanevax.org

- Over the past 2 decades pharmaceutical companies have gained unprecedented control over the evaluation and registration of their own products ¹⁴. This fact is reflected in the poorly designed safety and efficacy trials for vaccines for which there is no accountability.
- This is particularly the case because many vaccines are licensed in the USA where vaccine manufacturers are legally free from ordinary tort liability ²³. Vaccines are a product that are described as ‘unavoidably unsafe’ and there is no onus on manufacturers to make them as safe as possible because they are free from liability ²³
- Parents must ask if they wish their children to be subjected to the risk from a vaccine that has not been proven to prevent cervical cancer when there is already a safe and effective PAP screening procedure that will still be required anyway ¹⁴.

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www.vaccinationdecisions.net

References:

1. International Agency for Research on Cancer (WHO), 1995, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, volume 64, Human Papillomaviruses
2. Pfister H (Ed.), 1990, Papillomaviruses and Human Cancer, CRC Press Inc, USA
3. Australian Government, Department of Health and Ageing, 2005, “Screening to prevent cervical cancer: guidelines for the management of asymptomatic women with screen detected abnormalities, NHMRC, National Screening Program.
4. Haverkos H, 2005, Multifactorial Etiology of Cervical Cancer: A Hypothesis, *Medscape General Medicine*, v 7 (4): 57
5. Australian Government, Department of Health and Ageing, Office of Health Protection, 2009.
6. Future II Study Group, 2007, Quadrivalent Vaccine against Human Papillomavirus to Prevent High-Grade Cervical Lesions, *The New England Journal of Medicine*, 356, 19, 1915 – 27.

7. Dayton L, 2011, The Australian, Ian Frazer's HPV vaccine may prevent cervical cancer, 19th June
8. Walboomers J, Jacobs M, Manos M, Bosch X, Kummer J, Shah K, Snijders P, Peto J, Meijer C, Munoz N, 1999, Human papillomavirus is a necessary cause of Invasive Cervical Cancer Worldwide, *Journal of Pathology*, vol. 189 p.12-19
9. Parkin DM, Bray F, Ferlay J, Pisani P, 2005, Global Cancer Statistics 2002, CA: A *Cancer Journal for Clinicians*, 2005; 55; 74-108
10. Australian of the Year Awards 2012, Australian of the Year 2006, <http://www.australianoftheyear.org.au/pages/page58.asp> visited November 2011
11. Clifford et al, 2005, Worldwide distribution of human papillomavirus types in cytologically normal women in the International Agency for Research on Cancer HPV prevalence surveys: a pooled analysis, *The Lancet*, Vol 366, Is. 9490,2005,Pages 991-998
12. Australian Government, NCIRS, Human papillomavirus (HPV) Fact Sheet, <http://www.ncirs.edu.au/immunisation/fact-sheets/hpv-human-papillomavirus-fact-sheet.pdf> updated March 2013
13. Merck Inc, Clinical Review of Biologics License Application for Human Papillomavirus 6, 11, 16, 18, L1 Virus Like Particle Vaccine (*S. cerevisiae*) STN 125126 GARDASIL), 2006 (June 8), manufactured by Merck Inc.
14. Tomljenovic L, Shaw CA, 2012, Too fast or not too fast: the FDA's approval of Merck's HPV vaccine gardasil, *Journal of Law, medicine and Ethics*, 40 (3):673-681
15. Moscicki et al 2010 in Tomljenovic L, Wilyman J, Vanamee E, Bark T, Shaw C, 2013, HPV vaccines and cancer prevention, science versus activism, *Infectious Agents and Cancer Journal*, 8:6
16. Herskovits B. 2007, Brand of the Year, *Pharmaceutical Executive*, 27 (2): 58-65
17. a) Brisson M, Van de Velde N, Boily MC, **Economic evaluation of human papillomavirus vaccination in developed countries**, *Public Health Genomics*, August(5-6) 2009, vol 12: p 343 -51
b) Choi YH, Chaoman R, Gay N, Jit M, Potential overestimation of HPV vaccine impact due to unmasking of non-vaccine types: Quantification using a multi-type mathematical model, *Vaccine*, 2012, vol 30: p 3383 – 8

18. CSL Limited, Research and Development, Recent Highlights, Gardasil
<http://www.csl.com.au/research-development/recent-highlights.htm> visited November 2011
19. Uniquet, Technology Investment and Licensing, Gardasil – Human papilloma Virus Vaccine, <https://www.uniquet.com.au/portfolio/gardasil-human-papilloma-virus-vaccine> visited November 2011
20. S.A.N.E Vax Inc. Safe, Affordable, Necessary and Effective Vaccines,
www.sanevax.org visited 28 April 2011
21. Shoenfeld Y and Agmon-Levin N, 2011, ASIA – Autoimmunity/inflammatory syndrome induced by adjuvants, *Journal of Autoimmunity*, 36 p. 4-8.
22. C Exley, 2011, Aluminium-based adjuvants should not be used as placebos in clinical trials, *Vaccine*, 29, no. 50: 9289
23. 1986 National Childhood Vaccine Injury Act in Habakus and Holland 2011, Vaccine Epidemic: how corporate greed, biased science and coercive government threaten our human rights, our health and our children, Center for Personal Rights Inc, Skyhorse Publishing, 306th St New York ch 1.
24. US Centers for Disease Control and Prevention (CDC), Vaccine Safety, Reports of Health concerns following HPV Vaccination,
www.cdc.gov/vaccinesafety/vaccines/hpv/gardasil.html visited Dec 2011.