Cervical Cancer and the HPV Vaccine

The Ministry of Health (MoH) announced on the 20th of July that the medicines regulatory authority, Medsafe, had approved the vaccine Gardasil® for girls as young as nine. The MoH has all but admitted that the licensing of the vaccine in New Zealand was rushed through. New Zealanders should be able to make an informed decision about this vaccine and not be coerced or frightened into think it is a "must-have" for themselves or their daughters without knowing more about the vaccine, what it can and can't do, whether or not HPV is the last word on the causes of cervical cancer and the actual risks of cervical cancer.

The following information is excerpted from the 3rd edition of *Investigate Before You Vaccinate: making an informed decision about vaccination in New Zealand*, due out in early September, 2006.

The developers of human papilloma virus vaccine are touting it as the first vaccine to prevent cancer, a moniker that was once attributed to the hepatitis B vaccine (and still is in some quarters[1]). Generally the medical community stopped calling the hepatitis B vaccine the first vaccine to prevent cancer when it was pointed out that there are plenty of other ways to get liver cancer besides hepatitis B infection, that being vaccinated against hepatitis B didn't stop vaccine recipients from getting liver cancer in some other way (these issues are worth keeping in mind as we consider the HPV vaccine).

So now we have a new vaccine that carries the "first vaccine against cancer" mantle.

Cervical Cancer

In New Zealand in 2000, 205 women were diagnosed with cervical cancer (a rate of 8.5 per 100,000 women) and 60 women died (a mortality rate of 2.5 per 100,000 women).[2] Between 1991 and 2000 the incidence of cervical cancer in new Zealand fell by 34.1% and the death rate by 45.7%. This fall in both morbidity and mortality can largely be attributed to the cervical cancer screening programme. Through the detection of abnormal cervical cells (using a pap smear) precancerous conditions can be detected and treated before the development of cervical cancer, thus reducing the incidence of, and mortality from cervical cancer.

The life time risk of cervical cancer is very low. Although there don't seem to be specific figures for New Zealand women, in the US, where cancer incidence is generally similar, the lifetime risk of developing cervical cancer is 0.75% or 1 in 133 women, and the lifetime risk of dying from cervical cancer is 0.25% or 1 in 400 women.[3]

While cervical cancer may be the second most common cancer in women in other parts of the world, that is certainly not the case in New Zealand, where it comes eighth behind breast, colorectal, skin (melanoma), lung, ovarian and uterine cancer and Non-Hodgkins lymphoma.[2]

It was long believed that cervical cancer was associated with sexual intercourse, because it is rare in women who have never had sex (e.g. celibate women such as nuns). Now it is the human papilloma virus (HPV) that is believed to be responsible, in part, for the development of cervical cancer. Dr Harry Haverkos from the US FDA Center for Drug Evaluation and Research writes that HPV play at least a major if not a necessary role in the development of cervical cancer.[4] He goes on to say that "many investigators acknowledge that HPV is not sufficient to induce cervical cancer" and one or more other factors are also likely in order to initiate the cancer:

> *"HPV can be found in a growing proportion of patients with cervical cancer, approaching 100%, but is not yet found in every patient with disease. Other factors, such as herpes simplex virus type 2 infections, cigarette smoking, vaginal douching, nutrition, and use of oral contraceptives, have been proposed as contributing factors."*

It is estimated that 75% of sexually active men and women have been exposed to HPV at some point in their lives. [3]

However, it is extremely important to note that some other factor is required to trigger the

development of cervical cancer, and the medical community doesn't seem to know quite what that is. And when you consider that as many as 75% of women are exposed to HPV at some point in their lives, yet only 1% on them go on to develop cervical cancer, it is very, very clear the HPV infection alone is not the problem. HPV infection ***does not*** kill people!

But, of course, the vaccine manufacturers could see yet another captive market just waiting for yet another vaccine to save them from a cancer fate. It would clearly be easy to brush over the less than impressive incidence statistics with a public campaign of fear. After all, they already have a recipe that had been used so successfully with the flu vaccine.

The Human Papilloma Virus Vaccine

The human papilloma virus vaccine is based on 15 years of work by Professor Ian Frazer, who leads the Cancer and Immunology Research Centre at the University of Queensland.

Frazer and Dr Jian Zhou were trying to develop a treatment for women already infected with HPV, and in the process developed a "fake" virus – the virus coating without the pathogenic material inside – which then became the basis for the vaccine.

Of course, the theory for HPV vaccines is just like any other – inject a bit of the virus and trick the body into thinking it is under attack. The body produces antibodies to fight the virus and then retains a memory so that if it genuinely comes under attack from the real virus it knows what to do and rids the body of the virus before it comes to any harm. But it isn't that simple.

It is widely quoted that the human papilloma viruses comprise a group of some 80 to 100 viruses of which about 30 are believed to be linked to cervical cancer. Of these 30, HPV 16 and 18 are the ones that do most of the damage; although the figures vary from one paper to the next, HPV-16 is believed to be found in around 50% of cervical cancer cases and HPV-18 in another 20%. Which leaves another 30% of cancers that are associated with one of the other forms of the virus. Which is where the aim to prevent cancer through vaccination gets a little tricky.

Dr Thomas Broker addressed a 1999 workshop on 'Evolving Scientific And Regulatory Perspectives On Cell Substrates For Vaccine Development' held by the US FDA.[5] On the topic of HPV he said:

> *"We have found a brand new HPV type for every 10 people that we have looked at. Philodelius and Ethel Michelle Diveres and zur Hausen and Shamen in European study of tutanius papilloma viruses have found a new papilloma virus for just about every other person they have looked at when they use the combination of nested PCR and DNA sequencing. Robbie Burke's group, Jill Polefski's group, have very comparable experiences looking at anal papillomas or female genital tract. It is my contention right now that instead of 80 HPV genotypes or 150 that have been officially named, that there probably are millions of variants, virtually a continuum."*

Which presents somewhat of a problem if you want to develop a vaccine, as he went on to point out:

> *"Well the real problematic thing for any clinical management, either vaccination programs or small molecule drugs, is this absolutely exploding number of virus types."*

Despite this problem at least two pharmaceutical companies have since developed a vaccine: Merck & Co have developed Gardasil®, a quadrivalent vaccine for HPV 6, 11, 16 and 18; and Cervarix™, a bivalent vaccine for HPV 16 and 18 developed by GlaxoSmithKline.

And as HPV is a sexually transmitted virus it makes "good sense" to vaccinate women while they are still girls, before they become sexually active. In order to get them before all are sexually active it means vaccinating them when they are 11 or 12 years old. Which also makes good sense to the manufacturers and the pro-vaccine agencies because this is also at an age when girls are not yet old enough to take responsibility for themselves and are largely unaware of their rights to informed consent; an age at which vulnerable parents wanting to do the best for the children as they enter their teens, and face the awakening of their sexuality, still have the right to make such decisions. An age before young girls find their voice and learn that they can say no!

Merck's HPV vaccine

Gardasil® is the quadrivalent HPV vaccine developed by Merck & Co. It is a genetically modified, recombinant, quadrivalent vaccine containing virus-like protein particles from HPV types 6, 11, 16, and 18 inserted in to yeast cells.

The vaccine also contains approximately 225 micrograms of aluminium as an adjuvant, 9.56 mg of sodium chloride and 0.78 mg of L-histidine.[6]

A number of clinical trials of the vaccine have been reported on in the medical literature since 2002. Efficacy was assessed in four Phase II and III trials involving 20,541 women aged 16 to 26 years with follow up for between two and four years.[6]

(Not only did Merck fund these trials, as would be expected, but in one of the Phase II trials ten of the authors were employed by Merck and the company has financial arrangements with several other authors.)

Gardasil® was submitted for regulatory approval in the latter part of 2005 and in May 2006 Merck & Co began it's campaign to have all children in the US vaccinated with it.[7] The US Census Bureau says there are 32 million pre-teens and adolescents in that country, a considerable market for the vaccine.

Unsurprisingly, on June 8, 2006, the FDA announced that it had approved Gardasil® for use in females aged nine to 26 years. The FDA emphasized "that the product does not protect women if they have already been infected with HPV" and said this "indicates the importance of immunization before potential exposure to the virus." However, they also admitted that the vaccine does not protect against less common strains of HPV that are also associated with cervical cancer and "routine Pap screening will therefore remain critical."

At the same time Merck & Co. announced that the vaccine would cost about US$120 per dose;[8] US$360 for the three doses required (approximately $600 in New Zealand currency at the June 2006 exchange rate).

Then on June 29, the ACIP recommended "the routine use of the human papilloma virus vaccine for girls (age) 11 to 12. The recommendations also include permissive use of the vaccine down to age nine and up to age 26."[9]

Gardasil® does have some competition in the form of GlaxoSmithKline's bivalent HPV vaccine Cervarix™, which has not yet been submitted to the US authorities for licensing, although GSK plan to file for approval in the US in late 2006, and filed for approval in Europe, Australia, parts of Asia and Latin America from March 2006.[10]

What's Wrong With This Picture

Both Merck and GSK claim very high efficacy for their HPV vaccines – between 90 and 100% effectiveness in preventing HPV infection and the development of precancerous lesions. So what is wrong with this picture?

If you dig a little deeper there are plenty of problems with this apparent wonder-vaccine, the "first vaccine to prevent cancer"!

Does HPV cause cervical cancer and will an HPV vaccine prevent cancer, or even reduce the incidence? The ability of these vaccines to achieve this remains to be seen, but it is difficult not to be more than a little skeptical, specially as there are doubts about the real role of HPV in the development of cervical cancer.

Merck has claimed that Gardasil® is 100% effective in preventing cervical cancer because none of the women in it's study group developed precancerous lesions on their cervix while 21 out of 5,258 women in the placebo group did (0.4%). Cervical cancer takes years to develop – it is rare in women under 35 and the risk increases with age. All this clinical trial proved is that it stopped women developing precancerous lesions over the 17 months of the study, not for the rest of their lives. At best this study suggests that the vaccine slows down the development of precancerous lesions.

A US Obstetrician Gynecologist, Dr Clayton Young, opposes the HPV vaccine and points out that:

> *"The vast majority of women clear or suppress the virus to levels not associated with CIN II or III* and for most women this occurs promptly. The duration of HPV positivity (which is directly related to the likelihood of developing a high grade lesion or cervical cancer) is shorter, and the likelihood of clearance is higher, in younger women.*
>
> *Therefore, vaccinating these children against HPV with a vaccine that is of unknown duration of efficacy will only postpone their exposure to an age which they are less likely clear the infection on their own and be subject to more severe disease. This would require an unknown number of boosters and is a setup for complacency in the older population that is a recipe for disaster. Furthermore, the likelihood for regression to a normal pap*

* Cervical Intraepithelial Neoplasia are cancer precursor lesions and are graded as I, II or III.

> *from CIN II is 40%. This beats Gardasil's "best" reduction of CIN II-III of only 12%. In this case, "first do no harm" rules."*

Dr Young goes on to discuss the efficacy of the vaccine in the age group for which it has been approved:

> *"The study of the vaccine in children and adolescents is limited to only measuring the development of antibodies to the HPV subtypes in the vaccine. There is absolutely no evidence that the vaccine prevents anything when administered at this young age. Merck expects you to extrapolate their adult data to the immune response in children. If they were really interested in vaccine efficacy in children, should it not be studied properly in children?"*

We've already looked at Dr Thomas Broker's comments on the number of HPV viruses that may be circulating and the suggestion that constant mutation may up the number of viruses from about 100 into the thousands. However, another issue is that not all researchers in this area are convinced that HPV contributes in any way to cervical cancer.

Does HPV Really Cause Cervical Cancer?

In 1992 Drs Peter Duesberg and Jody Schwartz, molecular biologists at the University of California at Berkeley, questioned the increasingly popular idea that HPV plays a central role in cervical cancer.

They wrote that there is a "lack of consistent HPV DNA sequence and of consistent HPV gene expression in HPV DNA-positive tumors" in cervical cancer and pointed out that HPV is present in no more than 67% of age-matched women with cervical cancer, clearly demonstrating that cervical cancer can happen without HPV infection.[11]

This is a major "fly in the ointment" and one that seems to have been completely ignored by all those falling over themselves to add yet another vaccine to the schedule, including New Zealand's own IMAC who will discuss the HPV vaccine at their September 2006 Vision for Vaccines symposium.[12] IMAC also have a section on HPV vaccines and cervical cancer in their new 2006 *Immunisation Handbook* which indicates an intention that this vaccines should be added to the schedule in the near future.[12] The MoH has said that the vaccine will be considered in August 2006 for addition to the schedule when changes are next made in 2008.

Interestingly, Duesberg and Schwartz offer an alternative and entirely valid reason why HPV is associated with many cervical cancers saying:

"Since proliferating [cancer] cells would be more susceptible to infection than resting cells, the viruses would be just indicators, rather than causes of abnormal proliferation."[11]

But given our inherent and morbid fear of cancer, it is much easier to believe that we have found a cause and then a "cure", than to risk finding out we are no closer to knowing why some women get cervical cancer and why some don't, even though many lifestyle factors, particularly exposure to tobacco smoke (passive or active), are clearly also involved. And, of course, it is much more profitable for the pharmaceutical companies to have a vaccine mandated for children than for those same children to refuse to take up smoking.

Safety

When it comes to safety there are a number of concerns regarding Gardasil®. The Vaccines and Related Biological Products Advisory Committee, in their Background Document released immediately prior to their meeting that considered the licensing of Gardasil® states that they had two concerns that they identified during the efficacy review of Gardasil®:[13]

- that the vaccine may lead to an increased number of cases of a cancer precursor lesions among patients already infected by any of the four virus types at the time they receive the vaccine, and whose immune systems have not cleared the virus from their bodies. That is, that the vaccine may actually stimulate or trigger the development of precancerous lesions, if the recipient has already been exposed to those four HPV types.
- that any benefit offered by the vaccine is offset by a possible increase in precursor lesions or worse cases due to HPV types not contained in the vaccine.

In addition, during the clinical trials there were five cases of babies with congenital birth defects born to women who had 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.[13]

The participants in the study were followed up for 14 days after receiving either the vaccine or the placebo. There were numerous adverse reactions to both Gardasil® and the placebo, which is hardly surprising as some of the placebos also contained aluminium which is known to cause both localised injection site and systemic adverse reactions.

The impact of aluminium on localised or injection site reactions was clear:

	Gardasil® (N = 5088) %	**Aluminium Placebo** (N = 3470) %	**Saline Placebo** (N = 320) %
Injection Site			
Pain	83.9	75.4	48.6
Swelling	25.4	15.8	7.3
Erythema	24.6	18.4	12.1
Pruritus	3.1	2.8	0.6

From the Gardasil® datasheet.[6]

The percentage of participants who received Gardasil® who experience both mild to moderate and severe injection site reactions increased with each of the subsequent two doses, while such reactions decreased in frequency with both placebos. Some 60% of the participants that received either the vaccine or the aluminium containing placebo reported systemic reactions such as headache, nausea, diarrhoea, vomiting, fatigue, abdominal pain, dizziness and myalgia.[6]

Interestingly, the participants were followed up for auto-immune problems that may be related to the vaccine, a process that is very unusual for vaccine safety studies. Although the incidence of new medical problems were low in both groups over those four years there was a significant difference between the vaccine and placebo groups with three times the incidence of serious medical problems in the vaccine group. One case of juvenile arthritis, two of rheumatoid arthritis, five of arthritis and one of reactive arthritis were reported in the vaccine group.[6]

The reality is that until the vaccine is being used and adverse reaction reports start coming in, no-one has an accurate idea of how many adverse reactions there will be or how serious. If Gardasil® is administered together with other vaccines such as the adolescent DTaP it is going to be even harder to assess the overall impact of this vaccine on children's short and long term health.

Cost Benefit and Lasting Immunity

One big issue is the cost:benefit ratio, and at the moment it is not looking too good. Even if we ignore issues of whether or not HPV causes cervical cancer, this vaccine is very, very expensive. At the exchange rate at the time of writing, the three doses of Merck's Gardasil® will cost us $600 per 11 or 12 year old girl – approximately $16.5 million a year to vaccinate all eligible girls in New Zealand.*

Even if this vaccine works, and assuming for a moment that HPV definitely does cause cervical cancer, it won't wipe out cervical cancer. It contains only two of the viruses thought to be responsible for about 70% of cervical cancer. What about the other 30%? Even the "inventor" of the vaccine, Professor Ian Frazer, says this doesn't mean that pap smears and the cervical cancer screening programme can be consigned to the history books.[14] Women will still need to have regular smears, and as there is no other way of telling what HPV type a woman might have been infected with, all of them will need to be screened. On top of the cost of the vaccine!

In fact, one doctor expressed his concerns to the *Herald on Sunday* about possible complacency once a vaccine is introduced. The *Herald* reported that he "worries about the possibility a fix-it jab will make women think, incorrectly, that they no longer need to have regular pap smears. Another raises questions about whether, further down the track, the virus might mutate and fight back."[15]

The other point is that no-one knows how long any vaccine conferred immunity will last. It may not be long, perhaps five to ten years if many other vaccines are anything to go by. If your daughter is vaccinated at 11 then by the time she becomes sexually active, or at least soon after, her immunity may have waned to the point that she has no protection. The manufacturers and regulatory agencies have no idea at this stage how long any immunity will last. Will she know that? Will she have been told what else she can do to protect herself, or will she have been told "It's okay, you've been vaccinated, you're protected against HPV and cervical cancer."

And if boys are not vaccinated, there will be no chance of reducing the circulation of the virus in the community, those two strains of HPV – 16 and 18 – will still be out there, just waiting until your daughter's immunity wears off.

* Based on a birth rate of 55,000 per year, half of which are girls.

One of the striking things about vaccination programmes is that, rather than admit that vaccines are not perfect, those who promote vaccines act like they will solve everyone's health problems. No one bothers to tell parents and their children what else they can do protect their children.

Other Options For Preventing Cervical Cancer

First, there is an alternative means of preventing, or at least reducing the risk of, contracting an HPV infection. A study published in the June 2006 issue of the *New England Journal of Medicine* found that the consistent use of condoms offered considerable protection against HPV.[16]

Dr Rachel Winer and colleagues found that women whose partners always wore a condom during sex were 70 percent less likely to become infected with HPV than those whose partners used protection less than five percent of the time. In addition, the study found that, at the end of the eight month study, in women reporting 100 percent condom use by their partners, no pre-cancerous cervical lesions were detected, whereas 14 such lesions were detected among women whose partners did not use condoms or used them less consistently.*

But of course condoms aren't the same lucrative 'golden goose' for pharmaceutical companies that a vaccine is. Despite that fact that condoms have other health benefits such as protecting against other sexually transmitted diseases and pregnancy, they simply are not as profitable as Gardasil® will be for Merck.

Clearly not every woman gets cervical cancer. In fact, more than 99% of women don't develop cervical cancer. So, why not? Don't look to the pharmaceutical companies, regulatory agencies and pro-vaccine organisations to tell you, but it is there in the medical literature all the same. Like many other chronic diseases dietary deficiencies are implicated as causal factors. Selenium is one of those deficiencies and inadequate selenium has a role in the development of cervical cancer.

Research published in 2003 concluded that selenium and zinc deficiency may be risk factors. The results of the study "showed that the tissue contents of zinc, selenium, and calcium were significantly lower and the copper and iron concentrations and copper/zinc ratio were significantly higher in cervical cancer tissue than that for paired nonlesion tissue." In addition the blood levels "of zinc, selenium, calcium, and iron were lower and copper and manganese levels and copper/zinc ratio were higher in patients with cervical cancer than in healthy subjects."[17]

Another study, also published in 2003, got the same results: that significantly lower selenium and zinc levels and higher copper/zinc ratios were found in both CIN [Cervical Intraepithelial Neoplasia] and cancer patients compared with the controls."[18]

In addition, a 1993 paper reported that among a cohort of 15,161 women, low serum levels of total carotenoids, alpha-carotene and beta-carotene were a significant risk factor for cervical cancer. Smoking was also strongly associated with cervical cancer in this study.[19]

VACCINATION AND INFORMED CONSENT

In New Zealand health professionals have a legal obligation to obtain informed consent before vaccinating a child or adult. Informed consent can only be provided by a patient or caregiver (parent) when the patient or caregiver has considered **all** the information pertaining to the risks and benefits of vaccination.

There is pressure on health professionals to provide only information that is sanctioned by the Ministry of Health. However, "official" information is incomplete and it is recognised by New Zealand consumer advocacy and health organisations that further information is necessary in order for people to be able to make an informed decision.

INVESTIGATE BEFORE YOU VACCINATE
MAKE AN INFORMED DECISION

The Immunisation Awareness Society is a voluntary society, funded by membership subscriptions and donations.

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* Participants were either virgins or had had their first sexual intercourse within two weeks of the study commencing.

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