

GARDASIL VACCINATION: EVALUATING THE RISKS VERSUS BENEFITS

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All drugs are associated with some risks of adverse reactions and vaccines are no exception. In weighing risks versus benefits, one has to keep in mind that vaccines represent a special category of drugs since they are generally given to healthy individuals. If there are uncertain benefits from a vaccine, only a small level of risk of harmful effects may be acceptable. If the benefits are certain, then a greater risk of side effects may be tolerated. Here I review the current evidence which indicates that the former case, applies to Gardasil, the quadrivalent human papillomavirus (qHPV) vaccine:

- 1) The efficacy of Gardasil in preventing cervical cancer has not been demonstrated and the marketing campaign has been misleading. The efficacy of Gardasil remains unsubstantiated since the vaccine hasn't been adequately tested on the primary age group to which it is currently given.**

Merck promoted Gardasil primarily as a vaccine against cervical cancer, rather than promoting it as a vaccine against HPV infection or sexually transmitted diseases ¹.

According to recent reports published in two highly respected scientific journals, *Nature Biotechnology* and *Journal of American Medical Association (JAMA)*:

"Most genital infections are asymptomatic and resolve spontaneously, but the virus can persist and cause precancerous lesions that can become malignant over the subsequent 20-30 years." (*Nature Biotechnology*, 2007 ²)

"So how should a parent, physician, politician, or anyone else decide whether it is a good thing to give young girls a vaccine that partly prevents infection caused by a sexually transmitted disease (HPV infection), an infection that in a few cases will cause cancer 20 to 40 years from now?" (*JAMA*, 2009 ³)

The fact is that malignant cervical cancer takes decades to develop ²³ and yet the longest clinical trial on Gardasil was only four years in duration ⁴. In other words, Gardasil was never shown to prevent cervical cancer [emphasis added]. Furthermore, in all clinical trials conducted by Merck the cervical intraepithelial neoplasia (CIN) 2/3 precancerous lesion was used as the efficacy endpoint for evaluating the Gardasil ⁴. What is the problem with using the CIN 2/3 lesion as the standard for efficacy? First, **if the marketing claim for Gardasil is that the vaccine "protects against cervical cancer" ¹²⁵, then cervical cancer should have been used as the endpoint for efficacy, not a surrogate marker such as a CIN 2/3 precancerous lesion [emphasis added].** Second, in the natural course of cervical cancer, only a small fraction of the CIN 2 lesions will progress to CIN 3 lesions and only a small fraction of CIN 3 lesions will eventually progress to cervical cancer ⁶. Furthermore, even CIN 3 lesions are heterogeneous (there are early small lesions and old advanced lesions and we do not know what proportion of the small lesions, which serve as clinical endpoints in current studies, would persist to become large, advanced CIN3 lesions) ⁷. Therefore, in any female population (and that includes those who have undergone Gardasil clinical trials) there are many more CIN 2 lesions than a combination of CIN 3 lesions and cervical cancers. As a result, the vast majority of the "CIN 2/3 or worse" cases used for evaluation of efficacy, and listed in Merck's report to FDA Vaccines and Related Biological Products Advisory Committee (*VRBPAC Background Document on Gardasil HPV Quadrivalent Vaccine* ⁸), must have been CIN 2 lesions.

In a review of the literature from 1950-1992, it was noted that **60% of CIN 1 lesions regressed, 30% persisted, 10% progressed to CIN 3, and only 1% progressed to invasive cancer.** The corresponding approximations for CIN 2 were 40%, 40%, 20%, and 5%, respectively. The likelihood of CIN 3 regressing was 33% and that of progressing to invasive cancer was greater than 12% ⁶.

The author of the study, Andrew G Östör, MD, from the Departments of Obstetrics and Gynaecology and Pathology, University of Melbourne noted ⁶:

*“It is obvious from the above figures that the probability of an atypical epithelium becoming invasive increases with the severity of the atypia, but does not occur in every case. **Even the higher degrees of atypia may regress in a significant proportion of cases. As morphology by itself does not predict which lesion will progress or regress, future efforts should seek factors other than morphological to determine the prognosis in individual patients.**”* [emphasis added]

The above remark leads us to a third reason why a surrogate morphological marker is not an adequate endpoint for assessing the efficacy of cervical cancer vaccines ⁹:

*“**CIN 2 is not a true biologic entity but an equivocal diagnosis of pre-cancer, representing an admixture of HPV infection and pre-cancer. The existence of CIN 2 biopsy results as a clinical entity may be the consequence of the inaccuracies of colposcopy and colposcopically directed biopsy, which could result in less than-perfect representation of the underlying disease state.**”* [emphasis added]

Furthermore, the same report by the National Cancer Institute (NCI ⁹) states that:

“That CIN2 is the least reproducible of all histopathologic diagnoses may in part reflect sampling error...”

Finally, according to second report by the NCI ¹⁰:

“Approximately 40% of undiagnosed CIN 2 will regress over two years” (this also precisely corroborates the findings of the study by Östör)

Gardasil is marketed as the vaccine that prevents cervical cancer ¹²⁵. This statement is incorrect. Based on the above NCI findings, we can conclude that the data presented in the *VRBPAC Background Document on Gardasil HPV Quadrivalent Vaccine* ⁸ only supports the claim that **Gardasil can prevent “an equivocal diagnosis of pre-cancer, representing an admixture of HPV infection and pre-cancer” - about half of which are self-reversing to normal cases and do not reflect actual cervical cancer.** [emphasis added]

There was yet another important oversight in assessing the efficacy of Gardasil. Most cervical cancers are believed to be linked to infection with genital HPV types 6, 11, 16, and 18 ²³¹¹. According to NCI, the only reliable HPV genotyping method is a *“PCR system with short target sequences”* ¹² or alternatively, *“ ‘sentinel-base’ genotyping by PCR”* ¹³ Ironically, these HPV genotyping methods were never used to determine the HPV type associated with precancerous lesions in the clinical trials for evaluation of the efficacy of Gardasil to prevent type-specific HPV infections.

2) Cervical cancer is a rare disease in developed countries which invalidates the recommendations for universal immunization with any HPV vaccine. The incidence of cervical cancer has dropped substantially since implementation of regular Pap screening procedures. Currently, in the US, the death rate from cervical cancer (2.4/100,000 women) is lower than the rate of reported serious adverse events, including death, from Gardasil (3.34/100,000 doses distributed)

Although rare, the severity of cervical cancer should not be understated. Advanced cervical cancer is a deadly disease, especially in areas where the resources and infrastructure to fully implement Papanicolaou (Pap) smear tests are limited such as Latin America, Africa, India and South Asia ². **Regardless, in the past four decades, industrialized countries such as the US, have cut cervical cancer mortality and incidence rates by 74% largely through the use of the Pap smear** ² [emphasis added].

Thus, as noted by Diane Harper, MD, Professor and Vice Chair, Obstetrics and Gynecology, Community and Family Medicine and Informatics and Personalized Medicine, who conducted the phase 2 and phase 3 trials for Gardasil, authoring their publications, in developed countries such as the US, which have regular Pap screening programs in place, the HPV vaccine will do little to decrease the already very small cancer rate. In fact, Harper noted that **if women who are vaccinated stop going for Pap smears, the incidence rate for cervical cancer would increase**¹⁴. [emphasis added]

Based on L1-encoded virus-like particles, Gardasil should protect against the HPV genotypes 16 and 18, which are thought to account for 70% of cervical cancers². **Since Gardasil does not even claim to protect against all cases of cervical cancer but only those “caused by HPV strains 16 & 18”, it does not replace the need for a regular pap smear** [emphasis added].

More crucially, however, for deciding whether a risk of adverse effects from the HPV vaccine is worth taking, much depends on the perceived benefit from the vaccine relative to that risk. If benefits are indeed substantial, then many individuals would be willing to accept the risk. However, **if the benefit of the vaccine has not been demonstrated and is in fact only speculative, and if a majority of those women who are persistently infected with HPV are not likely to develop cancer providing they are adequately screened**²³, then most reasonably they will only be willing to accept very small risk of harm from the vaccine. **Data from clinical safety trials argue against small risks from Gardasil vaccination** [emphasis added]. In a paper published in *JAMA*, Slade et al. (2009)¹¹ report that from June 1, 2006, through December 31, 2008, the US Vaccine Adverse Event Reporting System (VAERS) received 12, 424 reports of adverse reaction following receipt of Gardasil amongst which, 772 (6.2%) were serious, including 32 deaths. Given the overall reporting rate of 53.9 reports per 100, 000 vaccine doses distributed¹¹, the estimated rate of reported serious adverse events from Gardasil is 3.34/100, 000 doses distributed. This rate is higher than the death rate from cervical cancer in the US which stands at 2.4/100, 000 women (according to CDC statistics,¹⁵

Harper poses an important question¹⁴:

“Would a parent accept such a rate of serious adverse events if the same cancer prevention can occur with continued Pap screening? Is there any acceptable level of risk of serious adverse events, including death, to prevent genital warts?” [emphasis added]

The later claim was in reference to one of the vaccine's other claimed benefits.

3) Most HPV infections are benign and resolve spontaneously without causing cervical cancer

According to Harper¹⁶:

“70% of all HPV infections resolve themselves without treatment within a year. Within two years, the number climbs to 90%. Of the remaining 10% of HPV infections, only half will develop into cervical cancer.”

These numbers are consistent with those above quoted from *Nature Biotechnology*²:

“Most genital infections are asymptomatic and resolve spontaneously, but the virus can persist and cause precancerous lesions that can become malignant over the subsequent 20-30 years.”

In addition, in a recent *JAMA* editorial, Charlotte Haug, MD, PhD, emphasized³:

“The virus does not appear to be very harmful because almost all HPV infections are cleared by the immune system. In a few women, the HPV infection persists, and some women may develop precancerous cervical lesions and eventually cancer. It is currently impossible to predict in which women this will occur and why. Likewise, it is impossible to predict exactly what effect vaccination of young girls and women will have on the incidence of cervical cancer 20 to 40 years from now.”

Thus, again, there appears to be little rationale in support of universal immunization with any HPV vaccine.

- 4) **Gardasil clinical trials, all conducted by the manufacturer, were inadequate and methodologically flawed. The risks of Gardasil vaccination are not fully understood since an inadequate placebo was used in clinical trials and the follow-up period was too short.**

In a safety evaluation study of Gardasil by Merck, the manufacturer used an inappropriate “placebo control” group in which results were pooled from a group that had received an aluminum salt adjuvant (amorphous aluminum hydroxyphosphate sulfate) together with the results from the group which had received conventional saline⁴. Altogether, bearing in mind that: **1) Gardasil is an aluminum-adjuvanted vaccine⁴, 2) aluminum is an experimentally demonstrated neurotoxin and¹⁷⁻²¹ 3) on the basis of previous research, a plausible support for a specific role of aluminum adjuvants in various neurological as well as autoimmune disorders in humans has been established²²⁻²⁶**, the rationale for such a “control-group” design remains tenuous [emphasis added]. In addition, the follow-up of trial participants was 2 to 6 months in duration⁴. During this period, a total of 245 adverse effects were reported in the group that received the vaccine compared with 218 for the “control” group⁴. Given that the aim of the study was to evaluate vaccine safety, the selected time frame should have been longer since potential auto-immune as well as neurological complications may take years to manifest^{27 28}.

Aluminum is a well demonstrated toxin in biological systems²⁹ whose more specific impacts on the nervous system have been extensively documented^{17 18 20 21 30-39}. **Common symptoms of aluminum intoxication in both animals and humans include: progressive dementia, diminished performance in learning tasks, speech impairments, loss of psychomotor control, twitches, tremors, jerks, seizures, behavioural changes (paranoia, confusion, psychosis) and, in extreme circumstances, death^{21 39}**. Of note, recent research demonstrates that **aluminum in levels comparable to those routinely found in vaccines can cause the death of motor neurons and induce impairments in motor function and decrements in spatial memory capacity** in mice^{17 36}. [emphasis added].

Consistent with the above experimental data, a host of neurodegenerative complications and diseases such as Alzheimer's^{21 38 40}, Parkinson's disease, amyotrophic lateral sclerosis (ALS;^{40 41}), multiple sclerosis (MS;^{23 42}), Gulf War Syndrome (GWS;^{25 26}) and epilepsy⁴³ have been linked to aluminum exposure.

In addition, **cases of motor neuron disease and multiple sclerosis (MS) after immunization with Gardasil have been reported⁴⁴**. All of these reports also indicate an **immune-mediated reaction which is not surprising given the immunostimulatory role of aluminum adjuvants²³⁻²⁵**. At the 134th annual meeting of the American Neurological Association in Baltimore, Oct. 11-14, 2009, researchers described a case of rapidly progressive disease leading to the death of a 14 year old girl. **Catherine Lomen-Hoerth MD, Director of the Amyotrophic Lateral Sclerosis at the University of California-San Francisco** reported the following⁴⁴:

*“Pathological features support the temporal association of the clinical presentation and vaccination and provides supporting evidence that **immune-mediated reactions to the nervous system are potential risks after Gardasil vaccination**. Our patient received three doses of Gardasil with symptom onset 2 months after her last dose. Despite treatment with aggressive immunosuppression, her weakness relentlessly progressed and **she died of respiratory failure 21 months after the onset of her weakness**.”* [emphasis added]

Post-mortem evaluations revealed widespread infiltrates of T lymphocytes and macrophages in the grey and white matter at all levels of the spinal cord. The researchers also reported **extensive demyelination (MS symptoms) and severe loss of motor neurons⁴⁴**. [emphasis added]

In September 2009, investigators presenting at the 25th **European Committee for Treatment and Research in Multiple Sclerosis** annual meeting **reported cases of autoimmune disorders after**

immunization with Gardasil. Lead investigator Maria Bouktsi from the Interbalkan European Medical Centre in Thessaloniki, Greece told *Medscape Neurology* that her team is questioning whether the **immunostimulatory effects of the HPV-like particles of the vaccine are triggering adverse effects in vulnerable patients**⁴⁴. It is the same question that researchers asked in a recent issue of *Multiple Sclerosis* (2009)⁴⁵. Ian Sutton, MB ChB(Hons), MRCP(UK), PhD, FRACP from St. Vincents Hospital, New South Wales, Australia, and his team have reported **five cases of multiple sclerosis after vaccination with Gardasil**⁴⁵. The team reported that patients presented with multifocal or **atypical demyelinating syndromes within 21 days of immunization**. These researchers have also noted that this was an **unusually rapid development of disease** that is not normally seen in the general population⁴⁵ [emphasis added].

In summary, a placebo group containing a demonstrated neurotoxic substance such as aluminum, invalidates the conclusion that Gardasil is not associated with a significant rate of adverse reactions (as claimed by the manufacturer, Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC)⁴⁶).

- 5) **Since 2006 when it was first approved, Gardasil has been associated with 20, 915 adverse reactions in the US alone. These included 89 deaths, over 1000 cases that required emergency hospitalization, and 382 abnormal pap tests**⁴⁷⁻⁴⁹. **Could the vaccine exacerbate the very disease it is claimed to prevent?**

VAERS is a passive and voluntary reporting system with only 1 to 10% of the population filing, according to National Vaccine Information Center (NVIC) estimates⁵⁰. For this reason, surveillance studies based on VAERS reports may grossly underestimate the true rate of adverse reaction from vaccines. If correct, this would imply that **Gardasil could be associated with as many as 200, 000 to 2, 000, 000 adverse reactions** [emphasis added]. Many people don't report to VAERS because they are not aware that the database exists and paradoxically, this includes doctors. According to Rosemary Mathis, mother of Lauren Brooke Mathis, who received her first Gardasil injection at the age of 13 years^{51 52}:

*"Prior to Gardasil, I did not know what VAERS was. When my daughter became ill, I found out about VAERS by research performed on the internet. My daughter's **doctors did not even know what it was** and they did not file a report until I filed one myself and told them **they were obligated by law to file a report**. How can the #'s be accurate if doctors don't file the reports? I even had to explain what VAERS is. Shouldn't VAERS and the adverse side effects of vaccines be taught in medical school or shouldn't the doctors receive periodic newsletters from the CDC explaining VAERS and its importance?"* [emphasis added]

According to the information from the FDA and the CDC on Gardasil and its Safety⁴⁶:

*"Since Gardasil was approved, the **great majority (94%) of adverse events** reported to VAERS after receiving this vaccine have **not been serious**. These reports **include syncope (fainting), pain at the injection site, headache, nausea, and fever**. **Fainting is common after injections and vaccinations, especially among adolescents**. Falls after syncope may sometimes cause serious injuries such as head injuries, which can be **prevented** with simple steps, such as **keeping the vaccinated person seated for up to 15 minutes after vaccination**." [emphasis added]*

The above claim suggests that fainting is apparently common with vaccines (especially among adolescents who incidentally, are targeted by this vaccine) and thus not a reason for concern. The statement by the CDC and the FDA also implies that simple prevention can resolve any potential resulting injuries. **It would also suggest that unless an adverse event is observed within 15 min of vaccination, it most likely did not occur as a result of Gardasil vaccination. This statement is misleading since neurological complications may take anywhere from weeks to years to be fully manifested**^{27 28}. As such, this claim by the CDC and the FDA effectively downplays safety concerns over Gardasil. This is a crucially important matter to consider since **recommendations by the FDA and the CDC profoundly affect practicing physicians**. According to parent's reports^{51 52}:

*“My 17 year old daughter, with prompting from her new adolescent pediatrician, received the first Gardasil vaccine on 4/23/09. She was told the side effects were: pain and redness at the injection site and possible fainting so she would **need to stay in the office for 15 minutes following the injection**. The next day, 4/24/09 she began having symptoms of dizziness, nausea and abdominal pain. On the 5th day of symptoms, we called the pediatrician and she said that **it could not be due to the Gardasil because it was too long past the injection and she felt it was viral.**” [emphasis added]*

It is obvious that physicians will not report to VAERS if they are not adequately informed on vaccine side effects. This not only leads to underestimation of case reports but also the inability to provide adequate treatment to those adversely affected by the vaccine:

*“On the 5th day of symptoms, we called the pediatrician and she said that it could not be due to the Gardasil because it was too long past the injection and she felt it was viral. We called the doctor again in June because the symptoms had progressed to: numbness and tingling to feet, joint pain, muscle weakness, stabbing pain to her back and feet, headaches, skin sensitivity, brain fog, chest pain, shortness of breath, racing pulse, extreme fatigue, visual disturbances. We saw the pediatrician and she referred us to Dr. Steven Linder, **neurologist... he diagnosed her extreme foot pain as peripheral neuropathy which was a result of the Gardasil vaccine. We sought the help from several different doctors who had little else to offer because they did not know how to deal with Gardasil side effects**^{51 52}.” [emphasis added]*

The above statement highlights the fact that the risks of Gardasil vaccination are not fully understood since the vaccine clinical trials were inadequate.

In recognition of this risk, Spanish health authorities have withdrawn tens of thousands of doses of a Gardasil vaccine after two teenagers who received the shots were hospitalized hours after receiving them⁵³. Similarly, in April 2010 the government of India called a halt to trials of HPV vaccine in the country. This followed reports of ethical violations within the trials and public outcry at deaths and side effects reported from use of the vaccine by a fact finding visit led by India’s civil society groups to the areas concerned⁵⁴.

In a recent letter to the editor of the *European Journal of Neurology* Svetlana Blithshteyn, MD of the Department of Neurology, State University of New School of Medicine and Biomedical Sciences, Buffalo , NY, US described a case of **Postural Tachycardia Syndrome (POTS) following vaccination with Gardasil**. POTS is thought to be an **auto-immune disease**⁵⁵. The symptoms include **dizziness, exercise intolerance, fatigue, nausea and loss of appetite**, which in this case has lasted months. The patient had no other relevant factors or events preceding the symptoms onset apart from Gardasil vaccination⁵⁵ [emphasis added]:

“There was no family history of cardiac, autoimmune or autonomic disorders. Other than vaccination with Gardasil 2 weeks prior to symptom onset, there were no other factors or events preceding the illness”

This is a significant piece of research as symptoms of **fainting and dizziness are the most common adverse event to Gardasil** and have been, somewhat dismissively, reported as “psychogenic”, as Blithshteyn remarks⁵⁵:

*“It is probable that some patient who develop POTS after immunization with Gardasil or other vaccines are simply **undiagnosed or misdiagnosed**, which leads to **under-reporting** and a paucity of data on the incidence of POTS after vaccination in literature” [emphasis added].*

Finally, the finding that **Gardasil was associated with abnormal Pap smears**⁴⁷⁻⁴⁹ **suggests that the vaccine in some individuals may exacerbate the risk for developing cervical cancer**. In fact, according to Merck’s *VRBPAC Background Document on Gardasil HPV Quadrivalent Vaccine*, the manufacturer **expressed “concern” regarding the administration of Gardasil to girls who are already affected with HPV strains 16 and 18**. Merck indicated that **if the cervical cancer vaccine was administered to such girls, it would increase their risk of developing cervical cancer by 44.6 %** (page 13, *VRBPAC*⁸). Despite this warning by Merck, **no screening is being done to rule out the presence of strain 16 or 18 of the HPV in girls before vaccination**. [emphasis added]

- 6) Gardasil contains sodium-borate (70 µg/mL) which, according to a 2005 listing at The National Library of Medicine (NLM) of the National Institutes of Health, is no longer commonly used in medicinal products due to its high toxicity⁵⁶. Symptoms of sodium borate poisoning include: collapse, seizures, coma, death, muscular spasms, dullness, lethargy, circulatory depression, central nervous system depression, kidney damage, nausea, vomiting, diarrhea, fever, low blood pressure⁵⁷.

Although boric acid was used to disinfect and treat wounds in the past, such practice was subsequently discontinued because patients who received such treatment repeatedly, got sick and some died⁵⁶. Boric acid is still contained in some vaginal suppositories used for yeast infections, however, this is not a standard treatment⁵⁶. Furthermore, at a recent **European Diagnostics Manufacturing Association (EDMA)** meeting, several new additions to the **Substance of Very High Concern (SVHC)** candidate list in relation to the Registration, Evaluation, Authorisation and restriction of Chemicals Regulations 2007 (REACH) were discussed⁵⁸. The registration and review completed as part of REACH has **changed the classification of Sodium Tetraborate CAS 1303-96-4 to: Highly Toxic⁵⁹. Sodium borate is commonly used in insecticides** and acute, accidental sodium borate poisoning usually occurs when someone swallows such products⁵⁶. Although large doses of sodium borate are needed for acute intoxication via ingestion exposure (Estimated lethal dose 15 to 20 grams⁵⁷), there is no data available on toxicity following injection exposure in humans [emphasis added].

Post-marketing surveillance data suggests that there is a common pattern of adverse reactions from Gardasil. **The following symptoms appear to be common among individuals who reported adverse reactions after they had received Gardasil: sudden fainting, collapse, seizures, pulmonary embolisms, difficulty breathing, paralysis, muscular spasms, memory loss, confusion, speech impairments, behavioural changes, fatigue, chest pain, arrhythmias, vomiting and diarrhea, dizziness, headaches, nausea, increased incidence of upper respiratory tract infections, vision problems, hypersensitivity to light, irritability, depression, and changes in menstrual cycle**^{11 44 51 52 55 60}.

- 7) Gardasil contains polysorbate 80 (100 µg/mL), a non-ionic detergent suspected to cause sudden unconsciousness, arrhythmias, chest pain, nausea, headaches, vomiting and diarrhea, dizziness, confusion, breathing irregularities, diminished resistance to infection and increased incidence of upper respiratory tract infections, in users of Darbepoetin Alfa, a drug which is also administered by injection⁶¹⁻⁶³.

Polysorbate 80 is a non-ionic surfactant used widely in foods, pharmaceutical preparations, and cosmetics because of its effectiveness at low concentrations and presumed relative low toxicity^{64 65}. **Darbepoetin Alpha** (brand name: Aranesp) which is normally given to chronic renal failure and cancer patients to treat anemia⁶⁵ (by stimulating the bone marrow to produce red blood cells), **contains 0.005% of polysorbate 80⁶⁶, which is half of the amount of polysorbate 80 in Gardasil (0.01%)⁴.**

In addition to suspected side effects cited above, studies have shown that polysorbate 80 at clinically-relevant concentrations (10-30 µg/mL, 10-3x less than the amount in Gardasil) increases the cytotoxicity of hydrogen peroxide *in vitro*⁶⁴. Result suggests that polysorbate 80 may increase the susceptibility of cells to oxidative stress because it decreases the cellular concentration of glutathione⁶⁴.

Polysorbate 80 may also affect fertility as indicated in a study by Gajdova et al. (1992⁶⁷). In this case, neonatal female rats were exposed to polysorbate 80 (trade name Tween 80) on days 4 to 7 after birth. **Treatment with polysorbate 80 accelerated maturation, prolonged the oestrus cycle and induced persistent vaginal oestrus in these rats.** The relative weight of the uterus and ovaries was decreased relative to the untreated controls. **Squamous cell metaplasia of the epithelial lining of the uterus and cytological changes in the uterus were indicative of chronic oestrogenic stimulation.** Ovaries were without corpora lutea and had degenerative follicles⁶⁷. Given that neonatal female rats were used in this experiment, the extrapolation of the study results to young female adults

exposed to polysorbate 80 may not be adequate. Nonetheless, **many adverse reactions from Gardasil include changes in menstrual cycle (including heavy periods, absence of periods, irregular cycle, severe PMS symptoms, etc.) which would suggest that the vaccine may interfere with female hormone levels, the ovarian cycle and subsequently-fertility.** In addition, some female users of Darbepoetin Alpha reportedly experienced abnormal menstrual cycles even after not having regular cycles for a long time⁶³. All of these outcomes are consistent with the effects of polysorbate 80 on neonatal female rats, hence the relevance of the study by Gajdova et al. (1992⁶⁷) should not be dismissed [emphasis added].

The use of non-ionic surfactants in biological systems aids drug delivery (by making water non-soluble drugs more bioavailable) since it has the effect of permeating cellular membranes^{64 65 68}. However, in addition to making a drug more bioavailable, **polysorbate 80 could also make potentially toxic components such as sodium borate and aluminum more bioavailable as well, thereby effectively lowering the toxicity threshold levels which are normally associated with administration of single compounds.** In other words, much smaller amounts of aluminum and sodium borate would be required to produce cytotoxicity if co-injected with a surfactant such as polysorbate 80. **Insofar there have been no studies to evaluate the systemic effects of co-administering three potentially toxic compounds (aluminum, sodium borate and polysorbate 80) via injection to animals or humans, hence, their administration via Gardasil to girls aged 9-26 years worldwide constitutes what can be considered as a big “public health experiment”** [emphasis added].

8) Professional medical association (PMAs) including the American College of Obstetricians and Gynecologists, the American Society for Colposcopy and Cervical Pathology, the Society for Gynecologic Oncologists, and the American College Health Association received funding from Merck in educational campaigns to promote vaccine use

A recent report in *JAMA* by Sheila Rothman, PhD, from sociomedical sciences and David Rothman, PhD, from social medicine, both at the Columbia College of Physicians and Surgeons, New York City, provides compelling evidence that Merck funded educational programs by PMA as a marketing strategy to promote vaccine use¹. In a reference to this paper, the accompanying editorial in *JAMA* states³:

*“The article illustrates how the Society of Gynecologic Oncology, the American Society for Colposcopy and Cervical Pathology, and American College Health Association helped market the vaccine and influenced decisions about vaccine policy with the help of ready-made presentations, slide sets, e-mails, and letters.... **These educational programs strongly promoting HPV vaccination began in 2006, more than a year before the trials with clinically important end points were published.** How could anyone be so certain about the effect of the vaccine? **This matters because the voices of experts such as the professional medical associations are especially important with a complex issue such as this.**”* [emphasis added]

Rothman and Rothman note¹:

“By making this vaccine’s target disease cervical cancer, the sexual transmission of HPV was minimized, the threat of cervical cancer to all adolescents maximized, and the subpopulations most at risk practically ignored.” [emphasis added]

“Rather than concentrating on populations in geographical areas with excess cervical cancer mortality, including African Americans in the South, Latinos along the Texas-Mexico border, and whites in Appalachia, the marketing campaign posited that every girl was at equal risk,”

*“The marketing campaign that followed, according to Merck’s chief executive officer, proceeded “flawlessly.”⁶ In 2006, **Gardasil was named the pharmaceutical “brand of the year” for building “a market out of thin air.”*** [emphasis added]

Merck had also bankrolled efforts to pass state laws across the US which would mandate Gardasil for girls as young as 11 or 12. In one such instance, Texas governor Rick Perry circumvented his state legislature and signed an executive order making HPV vaccination compulsory for 11- to 12-year-old girls. A report in *Nature Biotechnology* further adds ²:

“Adding fuel to the resulting outcry, it was revealed that Merck had contributed \$6,000 to Perry in the past and now employed Mike Toomey, a former Perry chief of staff, as its lobbyist. Surrounded by a chorus of disapproval, Merck cracked. As Nature Biotechnology went to press, the company announced a cessation of all efforts to lobby for US state laws requiring compulsory vaccination.” [emphasis added]

Merck’s marketing strategies were condemned even by those who were in favour of the vaccine:

“Merck is hammered for the fact that it is spending huge lobbying dollars to make the vaccine mandatory. Even those who strongly favor the vaccine, such as Dr. Joseph A. Bocchini, chairman of the committee on infectious diseases of the American Academy of Pediatrics, are stunned at the degree to which Merck has pushed its \$400 vaccine as a mandatory measure, rather than opting to phase in the vaccine at lower cost and with measures for informed consent and tiered pricing ⁵.” [emphasis added]

Similar marketing strategies were also seen in France where they were eventually stopped by the action of government health authorities. On August 31st 2010, **Merck’s marketing partner for Gardasil, Sanofi-Pasteur, was officially prohibited from advertising Gardasil for cervical cancer prevention in France.** The Director General of the French Agency for Safety of Health Products (AFSSAPS) **found the sponsor of several Gardasil ads to be in direct violation of French public health codes ⁶⁹.**

These violations included, but were not limited to: **1) Claiming longer efficacy than was actually proven.** *“The ads stated an 8.5 year efficacy period when, in fact, the only data of validated efficacy is limited to a maximum assessment of the effectiveness of 4.5 years”; **2) Making false claims:** the ads in question replaced the officially approved use of Gardasil for *“the prevention of low-grade lesions”* with statements indicating Gardasil be used for *“the prevention of pre-malignant genital lesions, cancers of the cervix and external genital warts.”* [emphasis added]*

According to the French Committee on Immunization Practices (CTV) and the High Council of Public Health (HCSP), *“the vaccines impact on the incidence and mortality of cervical cancer will only become apparent in the long term, in fifteen to twenty years ⁶⁹.”*

In spite of bad publicity, Merck’s business strategy suggests that the **manufacturer increasingly aims on expanding the market to include women ages 19 to 26, who have been less likely to get the vaccine ⁷⁰:**

“We see tremendous opportunity” said Bev Lybrand, Merck’s senior vice president of vaccines in a recent news report. *“We have a number of programs under way to get after these women.”* [emphasis added]

Further reports suggest that **Merck is counting on Gardasil to help offset declining sales of cholesterol drugs Vytorin and Zetia** after a study found they may work no better at unclogging arteries than a cheaper medicine ^{70 71}. There were also safety concerns over Zetia and the **manufacturer was accused of withholding important safety and efficacy information in an effort to protect sales ⁷¹.** Sales of the asthma treatment Singulair, Merck’s top-selling drug, have also slowed over safety concerns ⁷⁰.

“Gardasil needs to be doing better,” said Barclays Capital analyst Tony Butler in New York. *The vaccine “has become increasingly more important from a profit standpoint because of the concerns over Singulair and Vytorin and Zetia.”* [emphasis added]

SUMMARY: Clinical trials on Gardasil have been largely inadequate, the efficacy of the vaccine in preventing cervical cancer has not been demonstrated, the benefits of vaccination have been exaggerated and safety concerns downplayed, thus preventing parents from making informed decisions for their children. Routine immunization against cervical cancer with Gardasil is not supported by the current data. The benefit of vaccination is uncertain and the risks of serious adverse effects are substantial.

Gardasil can prevent “an equivocal diagnosis of pre-cancer, representing an admixture of HPV infection and pre-cancer” - about half of which are self-reversing to normal - **not cervical cancer.**

Most genital infections are asymptomatic and resolve spontaneously, but the virus can persist and cause precancerous lesions that **can become malignant over the subsequent 20-30 years.**

Merck’s longest median duration of follow-up in clinical trials: **4 years.**

Gardasil post marketing reports of adverse effects in the US according to VAERS:

20,915 adverse reactions

89 deaths

>1000 serious adverse reactions requiring emergency hospitalization

382 abnormal pap tests

Gardasil (polysorbate 80, 0.01%) adverse reaction symptoms: sudden fainting, collapse, seizures, pulmonary embolisms, DEATH, difficulty breathing, twitches and tremors, paralysis, back spasms, memory loss, fatigue, chest pain, arrhythmias, vomiting and diarrhea, dizziness, headaches, nausea, increased incidence of upper respiratory tract infections, vision problems, hypersensitivity to light, irritability, depression, and changes in menstrual cycle.

Darbepoetin Alfa (polysorbate 80, 0.005%): sudden unconsciousness, arrhythmias, chest pain, nausea, headaches, vomiting and diarrhea, dizziness, confusion, breathing irregularities, diminished resistance to infection, and increased incidence of upper respiratory tract infections.

Sodium borate: collapse, seizures, coma, death, muscular spasms, dullness, lethargy, circulatory depression, central nervous system depression, kidney damage, nausea, vomiting, diarrhea, fever, and low blood pressure.

Aluminum (“placebo control” in Gardasil clinical trials): progressive dementia, diminished performance in learning tasks, speech impairments, loss of psychomotor control, twitches, tremors, jerks, seizures, behavioural changes (paranoia, confusion, psychosis) and, in extreme circumstances, death.

“In addition, just as pizza bearing cheerleader drug reps are a poor substitute for medical education, pharmaceutical company lobbying is a poor substitute for well-reasoned public health policymaking⁵.”

References:

1. Rothman SM, Rothman DJ. Marketing HPV vaccine: implications for adolescent health and medical professionalism. *JAMA* 2009;302(7):781-6.
2. Flogging gardasil. *Nat Biotechnol* 2007;25(3):261.
3. Haug C. The risks and benefits of HPV vaccination. *JAMA* 2009;302(7):795-6.
4. Merck&Co Inc. Gardasil product sheet, date of Approval 2006, p. 1-26.
http://www.merck.com/product/usa/pi_circulars/g/gardasil/gardasil_pi.pdf
5. McGee G, Johnson S. Has the spread of HPV vaccine marketing conveyed immunity to common sense? *Am J Bioeth* 2007;7(7):1-2.
6. Ostor AG. Natural history of cervical intraepithelial neoplasia: a critical review. *Int J Gynecol Pathol* 1993;12(2):186-92.
7. Schiffman M, Rodriguez AC. Heterogeneity in CIN3 diagnosis. *Lancet Oncol* 2008;9(5):404-6.
8. FDA Vaccines and Related Biological Products Advisory Committee (VRBPAC) Background Document: Gardasil™ HPV Quadrivalent Vaccine. May 18, 2006 VRBPAC Meeting, p. 1-30.
www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4222B3.pdf

9. Castle PE, Stoler MH, Solomon D, Schiffman M. The relationship of community biopsy-diagnosed cervical intraepithelial neoplasia grade 2 to the quality control pathology-reviewed diagnoses: an ALTS report. *Am J Clin Pathol* 2007;127(5):805-15.
10. Castle PE, Schiffman M, Wheeler CM, Solomon D. Evidence for frequent regression of cervical intraepithelial neoplasia-grade 2. *Obstet Gynecol* 2009;113(1):18-25.
11. Slade BA, Leidel L, Vellozzi C, Woo EJ, Hua W, Sutherland A, et al. Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. *JAMA* 2009;302(7):750-7.
12. National Cancer Institute (NCI). HPV Genotyping. https://www.fbo.gov/index?s=opportunity&mode=form&id=da396b97ad6eb7ec4f7d511f85d9e325&tab=core&_cview=06, Accessed Jan 25th 2010.
13. Gharizadeh B, Zheng B, Akhras M, Ghaderi M, Jejelowo O, Strander B, et al. Sentinel-base DNA genotyping using multiple sequencing primers for high-risk human papillomaviruses. *Mol Cell Probes* 2006;20(3-4):230-8.
14. Chustecka Z. HPV Vaccine: Debate Over Benefits, Marketing, and New Adverse Event Data. *Medscape Med News* 2009. <http://www.medscape.com/viewarticle/707634>
15. Centers for Disease Control and Prevention (CDC). Cervical Cancer Rates by Race and Ethnicity (last reviewed: February 4, 2010). <http://www.cdc.gov/features/dscervicalcancer/>
16. Alliance for Human Research Protection (AHRP). Archive for the 'Dr. Diane Harper' Category, Correction for Gardasil Blog 117 from AHRP, Monday, November 30th, 2009. <http://easydiagnosis.com/blog/?cat=198>
17. Shaw CA, Petrik MS. Aluminum hydroxide injections lead to motor deficits and motor neuron degeneration. *J Inorg Biochem* 2009;103(11):1555-62.
18. Walton JR. Brain lesions comprised of aluminum-rich cells that lack microtubules may be associated with the cognitive deficit of Alzheimer's disease. *Neurotoxicology* 2009;30(6):1059-69.
19. Campbell A, Becaria A, Lahiri DK, Sharman K, Bondy SC. Chronic exposure to aluminum in drinking water increases inflammatory parameters selectively in the brain. *J Neurosci Res* 2004;75(4):565-72.
20. Bishop NJ, Morley R, Day JP, Lucas A. Aluminum neurotoxicity in preterm infants receiving intravenous-feeding solutions. *N Engl J Med* 1997;336(22):1557-61.
21. Exley C. Aluminium and Alzheimer's Disease: The science that describes the link. 1st ed. Amsterdam: Elsevier Science, 2001; p.452
22. Exley C, Swarbrick L, Gherardi RK, Authier FJ. A role for the body burden of aluminium in vaccine-associated macrophagic myofasciitis and chronic fatigue syndrome. *Med Hypotheses* 2009;72(2):135-9.
23. Gherardi RK. [Lessons from macrophagic myofasciitis: towards definition of a vaccine adjuvant-related syndrome]. *Rev Neurol (Paris)* 2003;159(2):162-4.
24. Gherardi RK, Coquet M, Cherin P, Belec L, Moretto P, Dreyfus PA, et al. Macrophagic myofasciitis lesions assess long-term persistence of vaccine-derived aluminium hydroxide in muscle. *Brain* 2001;124(Pt 9):1821-31.
25. Israeli E, Agmon-Levin N, Blank M, Shoenfeld Y. Adjuvants and autoimmunity. *Lupus* 2009;18(13):1217-25.
26. Agmon-Levin N, Paz Z, Israeli E, Shoenfeld Y. Vaccines and autoimmunity. *Nat Rev Rheumatol* 2009;5(11):648-52.
27. Authier FJ, Cherin P, Creange A, Bonnotte B, Ferrer X, Abdelmoumni A, et al. Central nervous system disease in patients with macrophagic myofasciitis. *Brain* 2001;124(Pt 5):974-83.
28. Classen JB. Childhood immunisation and diabetes mellitus. *N Z Med J* 1996;109(1022):195.
29. Carson BL. Aluminum Compounds. Review of Toxicological Literature, Abridged Final Report. Integrated Laboratory Systems, Research Triangle Park, North Carolina, 2000:84 p. http://ntp.niehs.nih.gov/ntp/htdocs/Chem_Background/ExSumpdf/Aluminum.pdf
30. Gies WJ. Some objections to the use of alum baking-powder. *JAMA* 1911;57(10):816-21.
31. Bowdler NC, Beasley DS, Fritze EC, Goulette AM, Hatton JD, Hession J, et al. Behavioral effects of aluminum ingestion on animal and human subjects. *Pharmacol Biochem Behav* 1979;10(4):505-12.
32. Banks WA, Kastin AJ. Aluminum-induced neurotoxicity: alterations in membrane function at the blood-brain barrier. *Neurosci Biobehav Rev* 1989;13(1):47-53.
33. el-Sebae AH, Abdel-Ghany ME, Shalloway D, Abou Zeid MM, Blancato J, Saleh MA. Aluminum interaction with human brain tau protein phosphorylation by various kinases. *J Environ Sci Health B* 1993;28(6):763-77.

34. Yokel RA, Allen DD, Meyer JJ. Studies of aluminum neurobehavioral toxicity in the intact mammal. *Cell Mol Neurobiol* 1994;14(6):791-808.
35. Fewtrell MS, Bishop NJ, Edmonds CJ, Isaacs EB, Lucas A. Aluminum exposure from parenteral nutrition in preterm infants: bone health at 15-year follow-up. *Pediatrics* 2009;124(5):1372-9.
36. Petrik MS, Wong MC, Tabata RC, Garry RF, Shaw CA. Aluminum adjuvant linked to Gulf War illness induces motor neuron death in mice. *Neuromolecular Med* 2007;9(1):83-100.
37. Platt B, Fiddler G, Riedel G, Henderson Z. Aluminium toxicity in the rat brain: histochemical and immunocytochemical evidence. *Brain Res Bull* 2001;55(2):257-67.
38. Walton JR. Aluminum in hippocampal neurons from humans with Alzheimer's disease. *Neurotoxicology* 2006;27(3):385-94.
39. Tomljenovic L. Aluminum and Alzheimer's disease: after a century of controversy, is there a plausible link? *Journal of Alzheimer's Disease* 2010;23(4), in press.
40. Perl DP, Moalem S. Aluminum and Alzheimer's disease, a personal perspective after 25 years. *J Alzheimers Dis* 2006;9(3 Suppl):291-300.
41. Perl DP, Moalem S. Aluminum, Alzheimer's Disease and the Geospatial Occurrence of Similar Disorders. *Reviews in Mineralogy & Geochemistry* 2006;64:115-34.
42. Exley C, Mamutse G, Korchazhkina O, Pye E, Strekopytov S, Polwart A, et al. Elevated urinary excretion of aluminium and iron in multiple sclerosis. *Mult Scler* 2006;12(5):533-40.
43. Exley C. Aluminium and Medicine. In: Merce ALR, Felcman J, Recio MAL, editors. *Molecular and Supramolecular Bioinorganic Chemistry: Applications in Medical Sciences*. New York: Nova Biomedical Books, 2009:45-68.
44. Gandey A. Report of Motor Neuron Disease After HPV Vaccine. *Medscape Med News* 2009. <http://www.medscape.com/viewarticle/711461>
45. Sutton I, Lahoria R, Tan IL, Clouston P, Barnett MH. CNS demyelination and quadrivalent HPV vaccination. *Multiple Sclerosis* 2009;15:116-19.
46. Centers for Disease Control and Prevention (CDC). Information from FDA and CDC on Gardasil and its Safety (Archived), 2008. <http://www.cdc.gov/vaccinesafety/Vaccines/HPV/HPVArchived.html>
47. Vaccine Adverse Event Reporting System (VAERS). VAERS data. <http://vaers.hhs.gov/data/data/>, Accessed Sept 5th 2010.
48. S.A.N.E. VAX, Inc. S.A.N.E Vax Objects to FDA Ruling for Gardasil Use for Anal Cancer in 9 to 26 year olds, December 27, 2010. <http://sanevax.org/blog/?p=1568>
49. Free Press Release. HPV Vaccine (Gardasil and Cervarix) VAERS Reports - Injury Statistics Increasing at Rapid Rate. December 13, 2010. <http://www.free-press-release.com/news-hpv-vaccine-gardasil-and-cervarix-vaers-reports-injury-statistics-increasing-at-rapid-rate-1292290323.html>
50. National Vaccine Information Center (NVIC). An Analysis by the National Vaccine Information Center of Gardasil & Menactra Adverse Event Reports to the Vaccine Adverse Events Reporting System (VAERS), February 2009. <http://www.nvic.org/Downloads/NVICGardasilvsMenactraVAERSReportFeb-2009u.aspx>
51. S.A.N.E. VAX, Inc. Gardasil/Silgard Victims from the United States. <http://sanevax.org/victims/gardasil-silgard-usa.shtml>, Accessed Jan 25th 2010.
52. Vaccine Information Coalition (VIC). Gardasil Injuries. <http://www.vacinfo.org/gardasil.htm>, Accessed Jan 25th 2010.
53. AFP. Spain withdraws cervical cancer shot after illnesses, Feb 10, 2009. <http://www.google.com/hostednews/afp/article/ALeqM5gIPeSOSkC3zU3Xd4HMRiovY9ri-Q>
54. Sarojini NB, Srinivasan S, Madhavi Y, Srinivasan S, Shenoi A. The HPV Vaccine: Science, Ethics and Regulation *Econom Polit Weekly* 2010;45(48):27-34.
55. Blitshteyn S. Postural tachycardia syndrome after vaccination with Gardasil (letter to the editor). *European Journal of Neurology* 2010.
56. Medline Plus, A service of the U.S. National Library of Medicine, National Institutes of Health (NIH). Boric acid poisoning, Update Date: 1/30/2009. <http://www.nlm.nih.gov/medlineplus/ency/article/002485.htm>
57. Mallinckrodt Baker Inc. Sodium borate, Material Safety Data Sheet (MSDS), Effective Date: 02/15/08. <http://www.jtbaker.com/msds/englishhtml/s3122.htm>
58. The European Diagnostic Manufacturers Association (EDMA). Comments for Annex XV SVHC Dossiers, Boric acid, Disodium tetraborate, anhydrous, Tetraboron disodium heptaoxide, hydrate. April 2010. http://echa.europa.eu/doc/about/organisation/msc/msc_rcoms2010/rcom_disodium_tetraborate_anhydrous/edma_comments_final.pdf

59. European Chemicals Agency. SVHC Support Document: Member State Committee draft support document for identification of disodium tetraborate, anhydrous as a substance of very high concern because of its CMR properties, June 2010.18.
http://echa.europa.eu/doc/candidate_list/svhc_supdoc_disodium_tetraborate_anhydrous_publication.pdf
60. Vaccine Information Coalition (VIC). Gardasil: Memorial Document.
<http://www.vacinfo.org/gardasil.htm>
61. Drug Information Online. Darbepoetin Alfa. January 5, 2011.
<http://www.drugs.com/cdi/darbepoetin-alfa-polysorbate-80.html>
62. Amgen Manufacturing Limited. Aranesp (darbepoetin alfa) For Injection, product information leaflet. Revised May 2010.
http://pi.amgen.com/united_states/aranesp/ckd/aranesp_pi_hcp_english.pdf
63. Rx List, The Internet Drug Index. Aranesp patient information including side effects.
<http://www.rxlist.com/aranesp-drug-patient.htm>, Accessed Jan 25th 2010.
64. Tatsuishi T, Oyama Y, Iwase K, Yamaguchi JY, Kobayashi M, Nishimura Y, et al. Polysorbate 80 increases the susceptibility to oxidative stress in rat thymocytes. *Toxicology* 2005;207(1):7-14.
65. Steele RH, Limaye S, Cleland B, Chow J, Suranyi MG. Hypersensitivity reactions to the polysorbate contained in recombinant erythropoietin and darbepoietin. *Nephrology* 2005;10:317-20.
66. Boven K, Knight J, Bader F, Rossert J, Eckardt K, Casadevall N. Epoetin-associated pure red cell aplasia in patients with chronic kidney disease: solving the mystery. *Nephrol Dial Transplant* 2005;20 (Suppl 3):33-40.
67. Gajdova M, Jakubovsky J, Valky J. Delayed effects of neonatal exposure to Tween 80 on female reproductive organs in rats. *Food Chem Toxicol* 1993;31(3):183-90.
68. Li GF, Tan YF, Guo D, Wang L. Effect of Tween-80 on the permeability of rhodamine 123, a P-gp substrate across rat intestinal membranes in vitro. *Nan Fang Yi Ke Da Xue Xue Bao* 2008;28(4):579-81.
69. Legifrance gouv., Le Service Public De La Diffusion Du Droit. Décision du 31 août 2010 interdisant une publicité pour un médicament mentionnée à l'article L. 5122-1, premier alinéa, du code de la santé publique destinée aux personnes habilitées à prescrire ou délivrer ces médicaments ou à les utiliser dans l'exercice de leur art.
<http://www.legifrance.gouv.fr/affichTexte.do;jsessionid=?cidTexte=JORFTEXT000022839429&dateTexte&oldAction=rechJO&categorieLien=id>
70. Bloomberg News. Merck Aims Gardasil to Women Least Likely to Benefit (Update2), October 17, 2008. <http://www.bloomberg.com/apps/news?pid=newsarchive&sid=am85Fd2sVycU>
71. Disability Insurance Resource Center. Canadians ingesting Ezetrol may be at risk. Updated March 17, 2008. http://www.lawyersandsettlements.com/case/ezetrol_heart_attack_stroke.html