

How Silencing of Dissent in Science Impacts Woman. The Gardasil® Story

Leonard F. Vernon

Spartanburg, USA

Email: drvernonchiro@aol.com

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Abstract

The issues of safety and efficacy of certain vaccines remains extremely contentious. The venues for this debate have included periodicals, documentary films, and an ever-increasing number of on-line sites. While debate in science is not only a common occurrence but a fundamental tenet of the scientific community, it only works when divergent opinions can be heard. When those who hold an opposing opinion are denigrated and/or marginalized by those holding the majority opinion such as in the issue of vaccination, where cultural authority for the issue is owned by the profession of medicine, both science and the public lose. What is often forgotten are the benefits derived from the questioning of drug safety that not only extends to the public but to physicians who rely on the truthfulness and accuracy of the information that is being supplied to them by manufactures and government agencies. While most physicians believe they are functioning in their patient's best interest when making vaccine recommendations, these recommendations by in large have become a matter of rote and are made because most physicians have bought into the "vaccines are safe" mantra. What most physicians don't realize is they have unknowingly been recruited by big pharma to assist in shutting down the vaccination debate. This suppression of vaccine opposition even among academics, is becoming more commonplace and will lead down a slippery slope that will silence opposition science, and the dangers that come with this. Those who question vaccine safety have been ostracized, misquoted and even made to appear mentally ill by those who hold the majority opinion on the issue. Physicians who question vaccine safety have had their licenses threatened or have been fired from positions. Tactics such as name calling and the use of terms such as pseudo-science, (even when the evidence being presented is from widely accepted peer-reviewed journals) or "conspiracy theorists" which has the effect of placing those holding the minority opinion in the category of such groups as 9/11 truthers, are not uncommon. Other methods of

curtailing the presentation of opposing vaccine views have included pressuring venues not to allow anti-vaccination proponents to appear, or using the media to “expose” anti-vaccination groups as “crack-pots” while simultaneously presenting the majority opinion and the presenters as the sole arbiters on the issue. The more extreme elements of the pro-vaccine group will even make the statement that the issue is settled and there is no need for discussion.

“Has there ever been a society which has died of dissent? Several have died of conformity in our lifetime.” Jacob Bronowski in *Science and Human Values*

Keywords

Vaccine Opposition, Human Papillomavirus, Vaccines, Adverse Reactions, Gardasil[®], Cervarix[®]

1. Introduction

What do 9/11 Truthers, those who believe that Paul was killed in a car accident and that the CIA is responsible for spread of AIDS have in common? They are part of the group known as conspiracy theorists. According to some, we can now add to this group those who question vaccine safety [1]. Published papers boldly labeling vaccine opponents as conspiracy theorist abound with titles such as: *The Effects of Anti-Vaccine Conspiracy Theories on Vaccination Intentions* [2] and *Trump Needs Vaccine Experts, Not Conspiracy Theorists* [3]. One web-site simply titled their headline, *The Vaccine Conspiracy Theorist* [4]. The use of the term clearly has the intent of being pejorative and demoralizing to the point that “ant-vaxxers”, as those who oppose vaccines or question vaccine safety are commonly referred to, are perhaps even mentally ill [5], referring to them as “loons” [6]. Some publications have resorted to the term, “the antivaccination cult” [7].

Publications such as Skeptical Science make no attempt to hide their contempt for the anti-vaccination movement calling its member “Kooks” [8]. The website Forward Progressives titled their vaccine story “A Shocking Truth Anti-Vaccine Nuts Don’t Want You to Know” [9]. Popular Science was just as blunt in their name calling by offering a guide on how to speak to anti-vaxxers entitled; “How to Argue with The Anti-Vaccine Crazy’s: A Guide” [10]. Another website just comes right out and calls this group ignorant. *“Talking to Anti-Vaxxers is almost pointless. They dig in their heels, shake their heads, and loudly cry, ‘Nuh-UH! They will cite absolute garbage to back up their claims. You won’t reach them, but you must face them down. Otherwise it will be easier for them to spout their ignorance again and again.”* [11]

Most health professionals, especially those in the pediatric community assume that anti-vaxxers are mainly hysterical parents or members of radical anti-medicine

groups that falsify data to gain support of their anti-vaccine mission. Those who oppose “anti-vaxxers” take an *a priori* approach to the issue believing there is no science to back up the “anti-vaccine” argument. This elitist attitude and effort to silence debate should be of concern to all scientists.

The vitriol with which vaccine opposition groups are attacked is not seen in any other dispute that involves questioning the safety of a medical procedure. The wholesale disregard for opposing views can be seen in statements such as this one by Pollard and Jacobson;

“Today, the spectrum of anti-vaccinationists ranges from people who are simply ignorant about science (or “innumerate”—unable to understand and incorporate concepts of risk and probability into science-grounded decision making) to a radical fringe element who use deliberate mistruths, intimidation, falsified data, and threats of violence in efforts to prevent the use of vaccines and to silence critics. Anti-vaccinationists tend toward complete mistrust of government and manufacturers, conspiratorial thinking, denialism, low cognitive complexity in thinking patterns, reasoning flaws, and a habit of substituting emotional anecdotes for data.” [12]

Similarly, writing on a blog under the pen name “Orac”, David Gorski, a surgeon and professor at Wayne State University in Detroit, has stated that; “*the concerns of these parents are almost always rooted in pseudoscience, fear-mongering, and outright scientific misinformation*” [13], a rather generalized and unsubstantiated statement, yet accepted as fact by most practicing physicians as well as most of the main-stream press.

This all-inclusive demeaning of vaccine skeptics defies logical explanation and is no longer limited to the likes of Jenny McCarthy, Robert DeNiro and other Hollywood luminaries. More recently these attacks have become personal with attacks on those in the academic community. Attempts at minimizing the authority or credentials of anyone who dare question the efficacy or safety of a vaccine, even when those doing the questioning have similar and often superior academic credentials are becoming more common place [14]. Martin describes this method of suppression thusly;

“When physicians and health authorities support vaccination based on careful assessments of benefits and risks, they may dismiss citizen critics as ill-informed. Because nearly all experts endorse vaccination, there may seem to be no rational basis for opposition. In this context, any physician or scientist who questions vaccination is a potential threat to the public perception that credentialed experts unanimously endorse vaccination. This sets the stage for suppression of dissent.” [15]

Tetyana Obukhanych, earned her PhD in Immunology at the Rockefeller University in New York and did her postdoctoral training at Harvard Medical School and Stanford University. Following the publication of an open letter to California legislators [16], who, at the time were attempting to enact a mandatory vaccine law and eliminating the philosophical exemption, she was attacked

personally and professionally [17]. Using a step by step process to explain how illogical the mandate that all children be fully vaccinated prior to enrolling in school was Obukhanych reiterated that the most often used argument against parents who choose not to vaccinate is that they endanger the rest of the public. It is this rationale that is behind most legislation to end vaccine exemptions. The problem here is that the nature of protection afforded by most vaccines recommended for children by the CDC is not consistent with this premise.

What Obukhanych explained and what most politicians, who believe they are acting in the best interest of their constituents don't understand, and likewise most physicians who are on the payroll of vaccine manufacturers either directly or by proxy choose to ignore, is that a substantial number of the recommended vaccines cannot prevent transmission of disease. This is because either they are not designed to prevent the transmission of infection (they are intended to prevent disease symptoms), or because they are for non-communicable diseases. People who have not received these vaccines pose no higher threat to the public than those who have. Clearly the point that Obukhanych was making was that the laws being introduced discriminate against non-immunized children in a public-school setting in the absence of scientific reason. Following the publication of the letter it wasn't long before the attacks on Obukhanych began [18].

Further attempts at silencing critics of vaccine safety can be seen as recently as 2016, when a peer-reviewed article published on January 9, 2016 in the online version of the journal *Vaccine*. The study, titled "*Behavioral abnormalities in young female mice following administration of aluminum adjuvants and the human papillomavirus (HPV) vaccine Gardasil[®],*" linked the human papillomavirus vaccine (HPV) Gardasil[®] to behavioral abnormalities. On September 24, 2015, the authors were notified by *Vaccine* editors that pending some revisions the paper was accepted for publication. The study was then accepted in revised form on December 15, 2015. In late January the paper was retracted, claiming, "*that the methodology is seriously flawed, and the claims that the article makes are unjustified*" [19]. The authors have accused the journal's editor, Gregory Poland, MD the Co-Director of The Vaccine Research Group at the Mayo Clinic of allowing a conflict of interest with Gardasil[®] manufacturer Merck & Co. to influence his decision to remove the paper from *Vaccine* [20]. Similar cases of retraction following publication of papers that raise the question of vaccine safety have recently occurred raising the issue of journal objectivity and independence [21] [22] [23].

In his doctoral dissertation James Rankin addresses the issue of why anti-vaxxers should not be summarily dismissed, saying;

"Some suggest conspiratorial thinking predicts a rejection of scientific evidence in the context of genetically modified foods, vaccinations, and climate science yet there is evidence the 'science' in each of these areas may not be so scientific. The potential for industry's influence over research outcomes is enormous. Financial incentives which might lead to corruption have been iden-

tified. Some have found industry-supported research impacts medical journal revenue. Indeed, raising questions about the legitimacy of the regulatory approval system and processes can bring oppression via self-censorship.” [1]

To back up his point Rankin cites a 2012 New York Times report that the Food and Drug Administration tracked the emails of scientists who raised questions about the agency to members of Congress and other authorities [24].

Admittedly there are extremists in the anti-vaccination movement, however, the painting of “all” vaccine skeptics with the same brush, and failing to respectfully examine dissenting views only serves to discredit the pro vaccine position. We have reached a point that as soon as one questions anything about vaccines—as soon as one expresses any doubt or concern about any vaccine practice—one risks being labelled an “anti-vaxxer”. I think that most would agree that if the issue were anything other than vaccines the data from the literature would be evaluated and objectively critiqued by physicians.

Unfortunately, not only for the public but for the average family physician and pediatrician the successful brainwashing pharmaceutical manufactures has caused most to take an “argument over, it’s settled” attitude when it come to the issue of vaccination. This has created a deeply embedded dogma while suppressing debate to suggest a different way of thinking. Even more disturbing is that most physicians are not even aware of the plethora of peer-reviewed scientific literature addressing safety and efficacy concerns of certain vaccines [25].

Challenges raised by anti-vaxxers are in most cases summarily dismissed with statements such as “...because of their inability to comprehend data correctly and then choosing to use only selective portions of such data” [26]. Unfortunately, even when opposing researchers point out glaring faults such as if population selection differed or alternate statistical methods were used even from the same dataset, that wildly different results could be the result they are routinely dismissed [27]. Accusations by vaccine researchers and vaccine manufacturers of data manipulation and selective data shopping by vaccine opposition groups are somewhat ironic, when data manipulation in an effort to obtain favorable outcomes is a technique that the pharmaceutical industry has been shown to use in obtaining FDA approval of various medications [28]. It should come as no surprise that distrust of both government [29] as well as pharmaceutical manufacturers is extremely high [30].

In attempting to explain to his peers how anti-vaxxers think Keelan argues that the continued effort to try and convince them of vaccine safety is a waste of time, “since theirs is a belief system that is rooted in a distrust of authority.” “Any attempt to increase compliance by a reiteration of the expert’s interpretation of risk ignores the social, institutional and cultural context in which the data itself is co-produced and this lies at the core of resistance. Resistance lies at the surface of a profound cultural skepticism in the autonomy, accuracy and vested interests of those producing data about vaccination” [31]. In other words, don’t waste your time telling anti-vaxxers repeatedly that vaccines are safe, this group

trusts no one. Since when in science is the questioning of those producing and presenting data a bad thing? Or does this only become an issue if the subject matter being discussed or questioned is vaccines?

With the pharmaceutical manufacturing industry's well documented historical background of fraud and deceit the real question is; Shouldn't physicians, men and women of science have some degree of skepticism? Shouldn't the intellectual curiosity of a physician be such that they would try and seek out the information opposing their own belief system?

Among the reasons that some physicians have chosen not to speak up could be fear of loss of license and/or livelihood or that showing the slightest sympathy for resister parents will mark him/her as a heretic? This is exactly what happened to Dr. Daniel Neides the medical director and chief operating officer of the Cleveland Clinic's Wellness Institute following the publication of an article questioning vaccine safety on the news website Cleveland.com. The Cleveland Clinic eventually issued a statement saying that Dr. Neides, will be "appropriately disciplined," and additionally posting an apology from Neides [32].

In 2015 the Arizona Board of Medical Examiners opened an investigation of Dr. Jack Wolfson, a cardiologist who has publicly questioned the safety and efficacy of certain vaccines. After a thorough investigation in a 4-1 vote the board ruled that they would take no action against Wolfson's medical license saying [33]:

"Thirty-eight people filed formal complaints, and many more called the board to informally voice concern about Wolfson's anti-vaccine evangelism. However, the board noted, no one has filed any complaints about the Scottsdale cardiologist's actual medical care."

2. Drinking the Kool-Aid®

Why, when the issue is other than vaccines, debate is alive and well in the medical community? Take for example statins. Even with the reported evidence that statins prevent premature death we don't stop investigating the safety and efficacy of these drugs? And, as we have seen from the additional studies the data have raised questions as to their safety and efficacy [34]. Do media reports with this conflicting data confuse the public, and cause some to make decisions to stop their medication without consulting their physician? Of course; but does this action make them a "kook"? Does questioning their physician about the drug's safety make them and others who question statin safety and efficacy a "*statin conspiracy theorist*"? While the questions are rhetorical, this is exactly what happens to parents or physicians who raise vaccine questions.

The pharmaceutical industry will tell the public and physicians that, "Vaccines are safe." "Vaccines are effective." "Vaccines save lives." But don't dare ask; How safe? How effective? How many lives? Should asking these questions be a reason to label a patient crazy or "problematic"? Is a physician who questions vaccine safety/efficacy a bad physician? Questioning makes the profession of medicine

stronger, not weaker. Yet the degree of questioning about certain vaccines from the average practicing physician appears to be minimal. Even when presented with valid scientific information from a concerned parent it is automatically assumed that the information must be from one of those “conspiracy websites.”

One item that consistently infuriates pediatricians and vaccine proponents is the mere mention of an association between vaccines and autism. This will almost instantly elicit the story of Andrew Wakefield, MD whose paper linking the MMR vaccine to autism was eventually retracted by the BMJ, with Wakefield later be labeled as a fraud [35]. Arguing the BMJ was right and Wakefield wrong, this does not dismiss the numerous other papers published in highly respected journals such as the *Journal of Toxicology* [36], the *Journal of Biomedical Sciences* [37], the *American Journal of Clinical Nutrition* [38], *International Journal of Toxicology* [39] that have drawn a link between vaccines and/or the adjuvants used in them and autism. Whether intentional or not, these papers are rarely if ever cited by vaccine proponents, with one author stating;

“The assertion that vaccine-autism concerns rest merely on spurious claims made by uneducated parents is in stark contrast with a large body of scientific literature. As mentioned previously, extensive research data has underscored the tight connection between development of the immune system and that of the CNS, and thus the plausibility that disruption of critical events in immune development may play a role in neurobehavioral disorders including those of the autism spectrum. Indeed, early-life immune challenges in critical windows of developmental vulnerability have been shown to produce long-lasting, highly abnormal cognitive and behavioral responses, including increased fear and anxiety, impaired social interactions, deficits in object recognition memory and sensorimotor gating deficits. These symptoms are highly characteristic of autism.” [40]

A common tactic of vaccine manufacturers is to accuse those who publish information questioning the independence and objectivity of vaccine efficacy and safety as perpetrators of fraud. Anti-vaccination groups have been accused of “... being driven mainly by ‘junk science’, litigious greed, hype and ego ...” [41]. It is statements such as these that elicit an instant visceral response from those who question vaccines, especially by those familiar with the pharmaceutical industry’s history. The historical data show that the pharmaceutical industry has often operated with a blatant disregard for human life in a culture of profit before safety. On many occasions, this was accomplished by utilizing outright fraud, making it all the more surprising how pharmaceutical company rhetoric can still be accepted by many at face value.

3. The Arthritis Relief Miracle

One needs to keep in mind that according to Jolley and Douglas “at the heart of the anti-vaccine conspiracy movement lays the argument that large pharmaceutical companies and governments are covering up information about vac-

cines to meet their own sinister objectives. According to the most popular theories, pharmaceutical companies stand to make such healthy profits from vaccines that they bribe researchers to fake their data, cover up evidence of the harmful side effects of vaccines, and inflate statistics on vaccine efficacy” [2]. What possible motive would this group have for such beliefs? Let’s look at some history.

Between 1999 and 2001 Merck’s patents on 5 of its bestselling drugs were set to expire, with an additional two more scheduled to expire in 2007 [42]. In need of a new best seller, (in the pharmaceutical industry a best seller is classified as any drug that grosses over \$1 billion in annual sales [43].) executives at Merck as well as their shareholders would look to the company’s new arthritis drug Vioxx, to fulfill this goal. They would not be disappointed. Vioxx was approved in 1999, and in 60 months’ over 107 million prescriptions were dispensed [44] to over 20 million Americans [45] with annual sales approaching \$2.5 billion [46]. But this financial gravy train came to a halt in 2004 when Merck “voluntarily” withdrew the drug from the market after it was concluded that there was significant evidence that the drug caused cardiovascular harm [44]. To the outsider this move had the appearance of a large pharmaceutical company being prudent and acting responsibly, however this was not the case.

Merck researchers raised concerns about Vioxx and its potential for cardiovascular harm in 1996 during the very early trial period, however when Merck submitted its data to the FDA any mention of cardiovascular events was excluded. The submitted trials involved small patient populations with low risk of cardiovascular issues with treatment periods that extended less than 12 months during which time researchers did not collect relevant outcomes to measure cardiovascular problems [47]. But as early as 1999 the company knew there was a problem.

In an effort to expand its FDA license for Vioxx Merck undertook the running of a randomized controlled trial known as the VIGOR study (Vioxx Gastrointestinal Outcomes Research) in the late 1990’s. The goal was to show that when compared to its competitor, naproxen Vioxx caused fewer gastrointestinal side effects [47]. To the excitement of Merck executives and its shareholders the study data which was presented to Merck’s safety board had yielded the results it had hoped for. Vioxx did in fact appear to be more forgiving on the gastrointestinal system, however what Merck neglected to present to its safety board in 1999 was data that indicated a 79% higher risk for serious cardiovascular problems or death. Additional scrutiny would later reveal that the chairperson of this “independent” safety board’s had family members who owned \$70,000 in Merck stock at the time. Other facts that were not disclosed included the fact that this consultant was awarded a two-year consulting contract before the study’s conclusion was disclosed [44]. When later questioned as to why Merck failed to disclose the cardiac information, Merck’s attorneys said, it was “only preliminary and thus potentially flawed.” Merck was only legally obligated to supply raw data

to the FDA and nothing more [42].

When in 2001 the study was published, in a classic case of data manipulation gastrointestinal issues were reported for one month longer than cardiovascular issues thus hiding the fact that during that month, additional cardiovascular events occurred, demonstrating the increased risk. Further manipulation occurred in the manner in which the data was presented. Naproxen was presented as the intervention group, only noting the relative risk, while failing to show the absolute numbers of cardiovascular events, while all other results were appropriately reported. Even data manipulation couldn't hide demonstrated a significant increased risk of myocardial infarction. But according to Merck experts this was not due to Vioxx, but a result of the "protective effect of naproxen against cardiovascular issues." It should be noted that this hypothesis was raised in the absence of any scientific evidence [44].

With the popularity of the drug at an all-time high in 2004 Merck again sought expansion of its Vioxx license and instituted the "APPROVe" (Adenomatous Polyp Prevention on Vioxx) study. The study was designed to measure the efficacy of Vioxx to prevent colorectal polyps. In this study, the authors while reporting an increase of cardiovascular events said these only occurred after 18 months of use.

Among the conspiracy theories that anti-vaxxers are often accused of promoting is that pharmaceutical companies apply pressure internally to silence their critics. However, as court papers would later reveal when FDA scientist David Graham examined the data from the VIGOR study by performing an epidemiological analysis on a population of 1.4 million his results showed that "27,000 heart attacks and sudden cardiac deaths could have been avoided" if the patients had used Celebrex (Merck's competition) instead of Vioxx. But these results were not made public and Graham and other researchers were "pressured to keep quiet." This pressure to silence dissent came not only from Merck, where senior management warned Graham he would face "serious consequences" if he continued to publicly express concerns over Vioxx [42], but from the FDA's Office of New Drugs, who, because they were not considering a warning against the use of Vioxx, suggested that Graham should change his conclusions about the drug [47]. When other researchers found similar issues as Graham and raised a red flag about Vioxx's safety, Merck responded by saying their data was flawed [46].

The FDA and Merck were not alone in their glossing over of the data on Vioxx. Co-conspirators included many journals, including the "New England Journal of Medicine", "Circulation", and the "Annals of Internal Medicine" all of which published articles favorable to Vioxx [44]. Additionally, Ross *et al.* found that many of these were ghostwritten by Merck staff or outside hired writers, while lead or sole authorship was attributed to an academic researcher [48]. It was further determined that in only half the of the ghostwritten papers was Merck's financial sponsorship disclosed. Even more astounding was that in

many cases it wasn't until the Vioxx lawsuits began did many of the "authors" of these papers become aware that they had in fact been listed as lead authors [49] [50] [48].

The marketing efforts did not stop with the falsified research reports. Merck, through an arrangement with academic publisher Elsevier created a series of fake journals [51]. Even though illegal and unethical methods were used to promote Vioxx, a drug whose dangers company officials were aware of, the billions of dollars at stake over road any moral compass the company or its officials may have had. Krumholz *et al* explain it thusly;

"With billions of dollars at stake, Merck conducted the trials, stored and analyzed the data internally, paid academic researchers as consultants to the investigative teams and the safety monitoring boards, and maintained heavy involvement in the writing and presentation of findings. The journals published the studies, and the academic community accepted the findings without expressing much concern." [44]

When it was eventually revealed that Merck's data was in fact flawed if not plain false the New England Journal of Medicine printed a correction. In September 2004, Merck "graciously" agreed to remove the drug from the market, but not until after it was responsible for between 88,000 - 139,000 heart attacks and strokes, 30% - 40% of which were fatal. By 2005 the media and Wall Street questioned the company's ability to survive, however reports of the company's emanate death were premature [47].

4. Enter Gardasil®: A Vaccine in Search of a Disease?

One of the most controversial vaccines that is being promoted to parents and physicians alike, is Gardasil®. It is astonishing why any physician would resist further investigation of the safety and efficacy of a product that is injected into literally millions of human beings, and in the case of Gardasil®, children. There is no shortage of peer reviewed literature that links Gardasil® to potential life threatening events such as postural orthostatic tachycardia syndrome (POTS) [52], as well as findings of CNS demyelination [53]. The literature documents several reports of development of autoimmune disease after human papilloma virus vaccination [54] [55] [56] [57] including autoimmune vasculitis [58], and the "mother" of the autoimmune diseases, SLE [57]. A recent advisory issued by the American College of Pediatricians warned of the potential of premature ovarian failure (POF) in young girls, with its significant consequences for future health and prospects of motherhood [59]. Individually these events could be dismissed as coincidental, however taken together, these indicate that at a minimum further study linking the HPV vaccine and an autoimmune response should be examined. Again, if the product being discussed were anything other than a vaccine would physicians be so cavalier in their dismissal of this information? Even if not convinced, certainly a more thorough evaluation of the patient for risk factors prior to administration of what is now looked at as a routine vac-

cine (there is nothing routine about it) should be done.

As of this writing there are three HPV vaccines marketed in the United States. They are Gardasil[®], Cervarix[®], and Gardasil 9[®] this will shortly become two, with the announcement of GlaxoSmithKline that they are no longer going to market Cervarix[®] in the US [60].

A brief history of HPV vaccines shows that Merck's Gardasil[®] (aimed at HPV types 6, 11, 16, and 18) was first approved in 2006 by the U.S. FDA for use with girls; however, males 9 - 26 years of age were added in 2009 to protect them from developing genital warts. On December 22, 2010, the FDA expanded Gardasil[®] approval to preventing anal cancer in both men and women 9 - 26 years old. The Advisory Committee on Immunization Practices (ACIP) recommended the routine use of Gardasil[®] in males as young as nine years old, with boys 13-21 years old eligible for the vaccine if they had not been vaccinated or completed the three-shot series. The committee also added that males 22 - 26 years old could elect to receive the HPV 4 vaccination [61]. On October 16, 2009, the FDA licensed bivalent human papillomavirus vaccine (HPV 2; Cervarix[®], GlaxoSmithKline) for use in females aged 10 through 25 years". Cervarix[®], is a bivalent vaccine that was aimed at protecting against two HPV types (16 and 18), protecting women against CIN 1-3 as well as cervical cancer [62].

In December 2014, the FDA approved Gardasil 9[®], for the prevention of certain diseases caused by nine types of Human Papillomavirus (HPV), five more HPV types (31, 33, 45, 52 and 58 which cause approximately 20 percent of cervical cancers) than original Gardasil[®]. As of October 2016, CDC and ACIP recommend that 11 and 12-year-olds receive two doses of HPV vaccine at least 6 months apart rather than the previously recommended three doses [63]. With GlaxoSmithKline withdrawal of Cervarix[®], and the last doses of original Gardasil[®] scheduled to be administered in May of 2017 Gardasil 9[®] will be the only HPV vaccine available in the United States, thus creating a virtual monopoly for Merck.

Increasingly, today's society has come to view many problems as medical disorders whereby medical interventions are the only appropriate solution, and thus the coining of the term medicalization. Conrad suggests that the "engines of medicalization", are "the pharmaceutical industry and market interests which are driving the conceptualization of disease by marketing illnesses to promote pharmacological solutions" [64].

Historical examples can be seen in the cultural shifts in thinking for ailments such as madness, alcoholism, and opiate addiction where the general thinking has shifted from deviant behavior or criminal acts to that of illnesses. By utilizing the technique of Medicalization, we are now able to legitimize social problems with the added benefit of providing a medical and/or a pharmacological solution, resulting in a proliferation and expansion of medical and diagnostic categories. Examples of such expansion can be seen in attention deficit hyperactivity disorder (ADHD), erectile dysfunction [64], childbirth [65] menopause

[66] and depression [67]. Many critics now view the process of medicalization as negative, calling it repressive, and coercive and arguing for the de-medicalization of various “medical” problems [68].

Accusations of “disease mongering” among pharmaceutical companies to increase profits have become more widespread [69]. Andrew Lakoff suggests that many diseases are increasingly defined in relation to the drugs to which it responds [70], causing him to suggest that because increased use of pharmaceuticals for purposes that are not strictly medical the more appropriate term should be Pharmaceuticalization [71].

In recent years there has been a shift in the characterization of risk factors to that of disease, with pharmaceuticals not only used to treat, but now possibly prevent disease [72]. The major beneficiary of this new “protodisease,” or predisease model has been the pharmaceutical industry who now rely on it as a major profit source [73]. Pharmacologist David Healy described this best when he said; “*drug companies obviously make drugs, but less obviously, they make views of illness*” [74].

In this new environment, the role of vaccines has increasingly changed in the new pharmaceuticalized environment from limiting infectious disease to treating non-infectious diseases such as various cancers, Type 1 diabetes, gastroesophageal reflux disease (GERD), Alzheimer’s disease, cocaine abuse and even cigarette smoking. It was in this environment that Gardasil[®] was created, and launched with a media campaign known as the “One Less” campaign where it was spun as both, “a drug against risk” and a vaccine [75] [76]. But what about the risks from Gardasil[®]?

Serious adverse events from a vaccine is defined by the FDA as those which “result in death, life threatening conditions, hospitalization, disability or permanent damage, birth defects, or require medical or surgical measures to prevent permanent damage” [77]. As even most pro-vaccine experts will admit almost all medical interventions carry some degree of risk that could cause a serious adverse event (AE), including Gardasil. But what is the frequency of these events? so the question is not whether Gardasil[®] has the potential to cause serious AEs but the frequency with which this occurs, information that is not always revealed to parents. As of 2015 serious adverse events (AE’s) following Gardasil[®] vaccination that have been reported in the medical literature include: premature ovarian failure [78], Guillian Barre syndrome and lupus and a host of other autoimmune related diseases [79], erythema multiform and other dermatological disorders [80], nervous system disorders such as POTS and many others [34], including death [81]. Most of these events are dismissed by pharmaceutical company experts as coincidental, occurring no more often then they might have with a placebo. Gardasil[®]’s safety record as presented by Merck to the FDA clearly showed its safety was not only as safe as a placebo but safer. It’s here that the waters begin to get a bit murky.

As all researchers know a placebo is a biologically inactive inert substance thus allowing the reaction of the control to be observed. While the results from clini-

cal trials of Gardasil[®] reportedly caused no more serious AEs than those of the placebo, further examination reveals a problem, the placebo used in the Gardasil studies was not inert.

Like most studies that involve vaccines the placebo used in the Gardasil[®] trials contained an aluminum based adjuvant “amorphous aluminum hydroxy phosphate sulfate” (AAHS). Adjuvants such as AAHS are routinely added to vaccines to increase the vaccines effectiveness and stimulate the immune system [82]. While the FDA has stated that up to 850 µg/dose of AAHS is safe, this is arbitrary and not based on safety evaluations but rather amounts that enhance a vaccine’s antigenicity [83]. Aluminum has been linked to a number of disorders of the nervous system GI tract including but not limited to multiple sclerosis, Crohn’s disease [84], Gulf War Syndrome, Alzheimer’s disease [85], autism and ALS [86]. So, without the use of a true placebo can the true safety of Gardasil[®] be evaluated?

In the only study that compared Gardasil[®] to a true placebo (saline) which can be found in the product insert, there was a 2 - 5 greater incidence of AE at the injection site than those in the placebo group [87]. While this is clearly an acceptable level of AE it is not the whole story. When presenting more serious AEs, Merck pooled the aluminum and saline placebo groups as one yielding a serious AE in the combined control and placebo groups with the same rate of serious AEs - 2.3 percent. This reporting mechanism should illicit a feeling of Déjà vu if one remembers Merck’s presentation of Vioxx safety data to the FDA. The choice to not separate the two “placebo” groups leaves the true safety of Gardasil[®] uncertain. Lacking any other explanation, one must at least wonder could it be that the unbundled data revealed Gardasil[®] had significantly more serious AEs?

The media and practicing physicians continue to regard Gardasil[®] as a relatively innocuous vaccine that has become routine, creating a comfort level and a false sense of security for both physician and parent. The reality is that this assumption is far from the truth. What becomes increasingly obvious when looking at vaccine safety data is that not everything is black and white. Data manipulation in the study of vaccines has become the norm. In a CDC and FDA funded analysis of the VAERS system Slade *et al.* found an increased rate of syncope and venous thromboembolic events, a finding that was minimized because the overall serious AE reported with Gardasil[®] were of no greater risk of than other vaccines [88]. So, case closed? Not so fast. Further evaluation of this report showed that 80% of Guillian-Barre syndrome (GBS) case reports to be of poor quality and were excluded thus leading to a gross underestimation of autoimmune disorders. Another disingenuous presentation of data from the study was the number of all AEs, this was compared against the number of doses distributed, the problem here is, not all distributed does are administered, so an accurate presentation of the safety data should use the latter [89].

Tomljenovic and Shaw undertook the task of presenting the data utilizing the

number of vaccine administered. The results were rather dramatic with the rate of serious AEs seven times higher than when calculated from distributed doses and 2.5 times higher than the US cervical cancer death rate of 1.7/100,000, at 4.3/100,000 [90]. In the U.S., there have been 59,092 adverse reactions reported VAERS since Gardasil and Cervarix were available in the United States. Of these adverse events, there have been 1727 reports of disability, 6388 listed as serious events, 9177 events where the individual has not recovered, and as of February 2017, 315 deaths reported [91]. Additional AE included 438 cases of abnormal pap smear, 143 cases of cervical dysplasia and 16 reports of cervical cancer. The rates of serious AEs per 100,000 showed a consistent pattern across various nations [90]. While acknowledging that VAERS data interpreted alone or out of context can lead to erroneous conclusions about cause and effect as well as the risk of adverse events occurring following vaccination it certainly, at the minimum should raise a red flag in the mind of any healthcare provider. One also needs to keep in mind that underreporting of vaccine reactions in the U.S. is a widely acknowledged weakness of VAERS. It is estimated that only between 1 and 10 percent of all adverse health outcomes which occur following vaccination are reported to VAERS [92] [93] [94].

Dr. Dianne Harper, widely recognized by her peers an expert on the subject of HPV and who helped design and carry out the Phase II and Phase III safety and effectiveness studies that led to Gardasil[®]'s approval now has reservations regarding its safety and efficacy. Harper has compared the level of serious adverse events from Gardasil[®] to Menactra[®], the meningitis vaccine which is known to have an increased risk of Guillian-Barre syndrome. She says:

“The tolerance for serious adverse events in a vaccine that prevents a disease that can kill within 24 hours after contracting the bacteria is different to the tolerance for serious adverse events in a vaccine that prevents disease from a virus that is mostly cleared by the body within 2 years of infection and does not progress to advanced stages of cancer unless there has been no screening for years. What tolerance level is acceptable?” [95]

Harper agrees that in countries where routine Pap screening is not available and mortality from cervical cancer is high, the risk of Gardasil[®] may be acceptable. However, in the United States where the majority of the population has ready access to Pap screening and a low incidence of cervical cancer there may be more risk from Gardasil[®] than HPV [95] [96]. Current estimations in the U.S. suggest that approximately 20 million women have some form of HPV, yet fewer than 12,000 are diagnosed with cervical cancer in a year and of those, less than 4000 will die of the disease. Cervical Intraepithelial Neoplasia, (CIN) which is abnormal cell growth on the cervix and which can lead to cervical cancer if left untreated, is classified as a rare disease by the National Institutes of Health. The disparity between the numbers of women who have HPV and develop cervical cancer suggest that only a small number of women have the strains of HPV that Gardasil[®] targets. Even more significant is the fact that while it's possible that as many as 5 percent of all cancers are associated with HPV infection, very few

people with HPV will ever be diagnosed with cancer, and with regular Pap smears, there is a greater chance of detection well before it progresses to malignant cervical cancer [97]. It is also well recognized that Women who smoke are about twice as likely as non-smokers to get cervical cancer [97]. A report the website Judicial Watch indicates that the group via a FOIA request reviewed correspondence between Merck and the FDA. Merck admitted that Gardasil[®] was found to *enhance* disease in recipients who already had “relevant HPV types” by 44.6 percent [98]. While the risk level may be acceptable to some, this acceptability is no doubt based on some guarantee of efficacy. But does such data exist?

Given its Vioxx history Merck’s promotion of Gardasil[®] as being 98% effective should awaken the senses of even the most ardent vaccine supporter. If one were to examine the clinical trial data they would instantly realize that the vaccine is far less effective than we are led to believe, even raising concerns with some researchers that it may lead to more severe infections and even an increased incidence of cervical cancer [99].

As is often the case in clinical trials for vaccines, because it is unfeasible or unethical to wait for the end-point disease to develop efficacy is determined using surrogate end markers. Epidemiologists hate surrogate variables because they introduce an additional step in the chain between intervention (or exposure) and outcome, and thus an additional source of potential error. To introduce surrogates means to increase uncertainty and, perhaps, an error. For a surrogate to be methodologically useful, it must be valid and measure what is theorized and it is here that issues starts to arise.

The surrogates in the Gardasil[®] trials involved mid-to-high grade cervical lesions, cervical intraepithelial neoplasia 2/3 (CIN 2/3). It is widely accepted that CIN 2 infections typically resolve on their own rarely progressing to cervical cancer. While CIN 3 infections may be a better marker, with Pap smears and treatment it too will eventually clear. Tomljenovic notes that the use of HPV of any severity is a poor marker for cervical cancer because most infections clear within 3 years [34].

In phase 3 randomized, placebo-controlled, double-blind studies, labeled the FUTURE I and FUTURE II studies, designed and funded by Merck, Gardasil[®] showed a 98% effective against HPV 16 and 18 CIN 2/3 women who tested negative for HPV at the beginning of the study. But is this presentation accurate or realistic? For this statistic to be true the potential treatment population would need to be vaccinated before beginning sexual activity, however many women will contract HPV before being vaccinated, thus making this efficacy rate disingenuous. Among all women in the study population ages 15 - 26, efficacy against CIN 2/3 was only 7.8% in the phase I trial 17% in phase II trials [100].

Another issue that researchers found problematic was the study’s finding of an increased rate of HPV 16 and 18 CIN 2/3 infections among HPV-positive vaccinated women. The seriousness of this becomes evident when one realizes that most women are not tested for HPV prior to vaccination [101]. While this

information was included in the VRBPAC document reviewed prior to Gardasil[®]'s approval, noting "*concern that subjects who were seropositive and PCR-positive for the vaccine-relevant HPV types had a greater number of CIN 2/3 or worse cases*" it was addressed no further [102].

In post-licensure data Gardasil[®] was shown to be 100% effective against HPV 16/18 CIN1-3 lesions. While at first glance this may appear impressive one needs to keep in mind that these data were a combined efficacy against HPV 16/18 CIN1-3. CIN1 is the lowest grade cervical infection, a majority of which clear on their own with only 1% of progressing to cervical cancer. In most cases the individual never even knew they had an infection. This raises the question; If we recognize that CIN2 is a weak surrogate, why even include CIN1 in the data analysis [34]?

According to Diane Harper a principal investigator in the Gardasil[®] phase II and phase III study Gardasil[®] will only yield a public health benefit against cervical cancer if 90% or more sexually active females are vaccinated, and if the vaccine is effectiveness is at least 15 years, however this is not the case. Studies show that there is a sharp decline in HPV 18 antibodies, and by year 5 post vaccine it cannot be detected in 35% of women [103] [104]. A girl vaccinated at age 9 or 10, long before she becomes sexually active, may not be protected against HPV 18 by the time she begins sexual activity [105]. While the overall efficacy against cervical cancer appears low, the true result remains uncertain as the time frame from Gardasil's FDA approval till now may be too soon for a cancer to develop.

5. Marketing Gardasil[®]

As of June 30, 2015, the producers of Cervarix[®], and Gardasil[®] are estimated to have sold 57 million and 190 million doses, respectively [106] for approximately 25 billion USD in total [107]. A 2013 report in Forbes magazine online points out that Merck spent, "just shy of \$44 million" to promote Gardasil[®] in 2012 and that this was less than in previous years such as the \$59 million spent in 2009 and nearly \$93 million in 2008 [108]. While physician and direct to consumer marketing have been successful avenues for the vaccine, even more successful for Merck was its lobbying efforts in state legislatures.

In February 2007 Texas Governor and future presidential candidate Rick Perry issued an executive order mandating a school entry HPV vaccination program for the states female students. The law raised a number of red flags including the fact that Merck had contributed \$5000 to the governor's campaign fund and that the governor's chief of staff had, previous to his employment by the state, worked as a paid lobbyist for Merck. In addition, there was the larger ethical question of the appropriateness of the vaccine manufacturer being so heavily involved in vaccine policy making.

Public outcry would cause Merck to announce it was suspending lobbying efforts for state mandates, this however was not entirely true. While decreasing its

very visible lobbying efforts a subtler form of lobbying was taking place, the implementation of legislator “education” programs and the funding of vaccines.

The vehicle that Merck would use to target legislators in Texas as well as in other states was through Women in Government (WIG), a national, nonprofit group of female state legislators. WIG had identified cervical cancer as a priority issue for the organization and Merck responded to this effort by contributing unrestricted educational grants to the group. Because there were no restrictions placed on the funds among other things they were used to cover the expenses of dozens of legislators to attend conferences on cervical cancer at appealing destinations all of which were attended by Merck representatives.

In addition to hosting meetings the group convened a task force that would issue recommendations to legislators as well preparing a “legislative toolkit” that among its contents was as a model of school-entry mandate legislation. Students of lobbying and politics have recognized how well Merck prepared the political environment for the introduction of school entry mandates and other legislation. Most of the mandate bills introduced in various states across the country were drafted by Merck through its proxy WIG [109].

Mark Largent, who labels himself pro vaccine, and who has coined the term “vaccine-anxious” parents, refuses to see public-health vaccine recommendations as a purely scientific prescription. He calls the recommended childhood vaccination schedule “a political artefact”—not a simple blooming of the science but a wrangled set of mandates and recommendations that it is not unreasonable for parents to question [13].

At the same time as these legislatures “education” events were taking place Merck conducted extensive outreach to the prescriber community, both directly and by training physicians to engage in peer-to-peer education. A marketing method that caught the eye of a California governmental official who related a historical analogy concerning Fosamax, Merck’s drug for prevention of osteoporotic fractures, who noted: “*They created this paranoia about fracture risk and applied it to a much bigger market. I think that they very successfully did the same thing with Gardasil[®]. They pumped up the level of fear among clinicians about the impact of HPV.*” In his book on bioethics, Glenn McGee, Ph.D. the founder of The American Journal of Bioethics addressed the Merck lobbying tactics from an ethical standpoint by saying, “*...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 policymaking.*”

In 2013 Merck again attempted to expand its user base with the publication of a Merck funded study. The new target group was over 24 sexually active females. While it is well established that most females by age 24 have already been exposed and there is little scientific evidence that shows protection from further infection if the vaccine is given after beginning sexual activity, Merck’s efforts to offer this group “potential protection” has begun. It should come as no shock that the competing interests section of this paper disclosed the following.

Competing Interests: M. Gonzalez and J. Luna have grants via their institution to serve as an investigator and colposcopist of protocol 019. J. Luna has received honoraria from Merck, Sharp & Dohme and Abbott Labs and support for travel from Instituto Nacional de Cancerologia. I. Maldonado and M. Plata have received grants through her institutions for board membership (IM), study conduct (IM & MP), support for travel (MP). M. Plata has received honoraria from Fundacion Cardioinfantil. D. Radley, S. Vuocolo, R. Haupt and A. Saah are employees of Merck and may own stock and/or stock options. This does not alter the authors' adherence to all the PLOS ONE policies on sharing data and materials.

Recently the Washington Post weighed in on Merck's direct to consumer marketing of Gardasil[®], asking the question; is Merck using guilt to market its vaccine? Some critics of the ad have said that they are more like "bullying" and "super sketchy" while another described it as "... like Catholic and Jewish guilt combined ...". A Wall Street Journal report said that the CDC is now encouraging doctors to pitch the vaccine by emphasizing its cancer-fighting benefits rather than its ability to protect against sexually transmitted disease [110]. This recommendation has raised ethical issues with some in the medical community. In a recently published paper on the topic epidemiologists Velen and Yadgar said the following; *The ethical analysis of vaccine desexualization reveals a complex interplay of considerations related to utility, causation of harm, duty of transparency, right to know, and right not to know.* [111]

The goal of this commentary is not to examine each argument for or against the use of HPV vaccines, but given the far-reaching implications of risk versus benefit, to at least open a dialogue and acknowledge that there are in fact risks associated with the vaccine, death being one of them. It is hoped that instead of looking at parents who question the safety and efficacy of a vaccine such as Gardasil[®] as "kooks" that the physician, when deciding to vaccinate or not will ask the question; "Is there good evidence that this new vaccine is likely to make my patient live longer or better compared with the available alternatives?" [112] We do not know how long the vaccine will last, the HPV types covered by the vaccine are limited, and the very safe alternative of Pap screening with early detection and treatment is a proven successful program. Although Gardasil[®] may allow a woman to experience fewer abnormal Pap tests it is not likely to extend a woman's life in countries where cytology screening is readily available [113] [114].

It is my hope that instead of just accepting what is supplied as educational information the physician will take the time and not just drink the Kool-Aid, but look at competing data and raise a challenge if he or she feels compelled to do so, and to do it without risk or threat of governmental or institutional repercussion.

Conflict of Interests

The author declares that there is no Conflict of interests regarding the publication of this article.

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Abbreviations and Acronyms

AAHS: Amorphous Aluminum Hydroxy Phosphate Sulfate
ACIP: Advisory Committee on Immunization Practices
ACP: American College of Pediatricians
ADHD: Attention Deficit Hyperactivity Disorder
AE: Adverse Event
ALS: Amyotrophic Lateral Sclerosis
APPROVe: Adenomatous Polyp Prevention on Vioxx
CDC: Centers for Disease Control
CIN: Cervical Intraepithelial Neoplasia
CNS: Central Nervous System
FDA: Federal Drug Administration
FOIA: Freedom of Information Act
GBS: Guillian-Barre syndrome
GERD: Gastroesophageal Reflux Disease
GSK: GlaxoSmithKline
HPV: Human Papillomavirus
MMR: Mumps, Measles & Rubella vaccination
NIH: National Institutes of Health
POF: Premature Ovarian Failure
POTS: Postural Orthostatic Tachycardia Syndrome
SLE: *Systemic Lupus Erythematosus*
USD: United States Dollar
VAERS: Vaccine Adverse Event Reporting System
VIGOR: Vioxx Gastrointestinal Outcomes Research
WIG: Women in Government