University of Nevada, Reno

Evaluation of the Human Papillomavirus (HPV) Vaccine Utilization, Benefits, and Risks

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by

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ABSTRACT

The Food and Drug Administration (FDA) licensed the first two human papillomavirus (HPV) vaccines, *Gardasil* and *Cervarix,* for routine use among adolescent girls and young adult females in United States (U.S.). According to the manufacturers, both vaccines were developed to prevent cervical cancer. However, in the long history of the fight against diseases and since vaccines were developed as primary disease prevention tools, no vaccines have been more controversial than these vaccines.

Millions of doses of the HPV vaccines were distributed, however, the number of dose that have already been used is currently unknown; the characteristics of healthcare providers administering the vaccines, and the demographics of females who started or completed the three-dose series are not well described. Additionally, shortly after the commencement of population-based vaccination, questions arose as to whether these vaccines are effective in preventing cervical cancer. Also, major concerns about their safety, duration of protection, benefits, and cost-effectiveness were increasingly raised.

This research evaluated serious adverse events following vaccination with *Gardasil*, analyzed the characteristics of those who received the vaccine, and provided a thorough and objective assessment of the value such vaccine may add to the fight against cervical cancer. Extensive data mining, review and analyses of negative health events reported to the Vaccine Adverse Events System (VAERS) and several other large databases were performed on a weekly basis during the three-year study period from November 2006 to November 2009.

The disproportionate number of negative adverse events associated with *Gardasil* was significant when compared to other vaccines. Under the current safety profile, it

seems that the benefits of vaccination for an almost always harmless virus such as HPV do not outweigh the risks, and even rare adverse events in a perfectly healthy young girl may be too much of a risk.

The results of this study highlighted increasing rates of serious risks and negative health outcomes associated with HPV vaccination. Moreover, it also emphasized that immediate and long-term benefits of the vaccine seemed insignificant. Currently, the HPV vaccine is underutilized, has a questionable safety record, and is of unproven effectiveness, especially when compared to regular cervical cancer screening. However, even if *Gardasil* turned out to be less risky and more effective, this vaccine is very costly and will not reduce the risk of exposure to or contracting HPV infections. Additionally, it will not reduce the need for routine life-long cervical cancer screening and Papanicolaou (Pap) testing. Furthermore, its use will not impact the incidence or deaths associated with cervical cancer even if the protection against HPV genotypes included in the vaccine would outlast the decades-long latency period of invasive cervical cancer.

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INTRODUCTION

Two Human Papillomavirus (HPV) vaccines, *Gardasil* and *Cervarix* were recently licensed for use among teen-age girls and young adult females aged nine to 26. Both genetically engineered vaccines were designed to prevent two oncogenic cervical cancer-associated HPV genotypes. *Gardasil* can also prevent two non-oncogenic HPV genotypes 6 and 11 believed to be associated with genital warts.

HPV is the most prevalent sexually transmitted infection (STI) in America and worldwide, and so far there are at least twenty oncogenic and a hundred non-oncogenic HPV genotypes that were identified. Most of HPV infections clear spontaneously without any consequences. However, for some unclear, probably host-related risk factors few HPV infections may persist and advance to cervical displasia. Undetected and inappropriately managed displasia may advance to cervical cancer over a period of two to four decades.

Since vaccines were developed as primary disease prevention tools no vaccines were more controversial than the HPV vaccines. According to the manufactures both vaccines were developed to prevent cervical cancer. However, such an ambitious purpose was not demonstrated in the clinical trials that lead to FDA-licensure. On the other hand during these trials both vaccines demonstrated high efficiency in preventing two oncogenic HPV genotypes 16 and 18.

It is unclear if the HPV vaccine was originally developed to prevent HPV as a sexually associated infection or it was truly expected to prevent cervical cancer. Although both diseases are closely related, preventing one of them does not necessarily translate in preventing the other.

Soon after the commencement of population-based vaccination with *Gardasil* concerns started to emerge about the vaccine benefits, risks and duration of protection. One of the most challenging decisions for the public health and healthcare systems is to determine if a new intervention is reasonably safe especially when its effectiveness is not demonstrated, and no population based studies are completed yet.

Millions of *Gardasil* doses were already distributed. However, it is unknown who is accessing this vaccine, how many doses were used, and who is using it. When new medical interventions, including vaccines, are specifically geared toward otherwise healthy and young children even minimal risks may not be tolerated. As a new intervention that is aimed to prevent cervical cancer *Gardasil* was never compared to the already existing and established regular cervical cancer screening. Current population-based Papanicolaou (Pap) testing programs are already proven to be highly effective in preventing cervical cancer and other precancerous lesions of the uterine cervix.

So far there is no reasonable explanation on how preventing just two out of so many oncogenic HPV genotypes would result in preventing cervical cancer. Such unanswered questions and other gaps in defining the exact purpose of *Gardasil* provided the opportunity to evaluate this new medical intervention. We started this research just few weeks after the Food and Drug Administration (FDA) licensed *Gardasil* for use in the United States (U.S.) in June 2006. Although both vaccines *Gardasil* and *Cervarix* are very similar, we mainly focused our study on *Gardasil* because the use of *Cervarix* in the U.S. started after concluding our research activities.

Given the long and complex natural history needed for cervical cancer to develop, assessing the vaccine effectiveness and ability to provide long-lasting protection is not

feasible at this time. Such studies require long-term extensive population-based research and decades of prospective cohort epidemiological studies.

Our research suggested that *Gardasil* is less effective than the regular Pap testing in preventing cervical cancer mortality is underutilized, and its benefits do not outweigh its risks. Obviously the safety and utilization of a new intervention are interconnected. If the benefits of a vaccine do not outweigh its risks then healthcare providers and the public as well will not be so eager to use it.

For the purposes of this research we considered the most favorable assumptions regarding the vaccine effectiveness in preventing HPV genotypes 16 and 18, and its long-lasting protection. To accomplish this near real-time cross-sectional study we conducted extensive literature review, electronically accessed several national and state key data systems, and used innovative epidemiological designs and study approaches to complete the following three interconnected original studies:

1. Compared the HPV vaccine potential to reduce cervical cancer mortality with observed performance of regular cervical cancer screening.
2. Compared serious and fatal adverse events following *Gardasil* with the mortality associated with cervical cancer.
3. Analyzed the HPV vaccine utilization among those enrolled in the Vaccines for Children (VFC) Program in Nevada.

It is important to emphasize that three years of population-based use of the vaccine is by no means enough time to measure its impact on preventing cervical cancer; especially when it takes at least thirty years for an undetected invasive and fatal cervical cancer to

develop and advance. Our methods, assumptions, findings, limitations and lessons learned are described in details in the following chapters.

CHAPTER 2

HUMAN PAPILLOMAVIRUS VACCINE CONTROVERSY OVER RISKS AND BENEFITS

ABSTRACT

Two Human Papillomavirus (HPV) vaccines were recently licensed for use among teen-age girls and young adult females in the U.S. and the European Union. According to the manufacturers both genetically engineered vaccines, *Gardasil* and *Cervarix*, were developed to prevent cervical cancer. However, after approximately three years of population-based implementation, questions have been raised as to whether these vaccines are effective, as well as major concerns about their safety, duration of protection, benefits, and cost-effectiveness. This research provides a thorough and objective evaluation of these new HPV vaccines and assesses the value they may add to the fight against cervical cancer.

To evaluate the performance of the HPV vaccines we compared the number of lives that are saved due to regular cervical cancer screening with the number of lives that could be potentially saved due to the HPV vaccine. The number of lives saved due to regular Pap test screening was calculated based on the average annual rate of decline in cervical cancer mortality (4.2%) observed in the U.S. The number of lives that could be saved due to the HPV vaccine was estimated based on findings from clinical trials that preceded the Food and Drug Administration (FDA) licensure for *Gardasil.*

Under the most favorable assumptions regarding the vaccine complete effectiveness and duration of protection it was projected that *Gardasil* may have the potential to prevent up to 49% of cervical cancer deaths among those who were originally naïve for the HPV vaccine genotypes 16 and 18. Subsequently, about 441 lives could be saved due to the vaccine, in the thirtieth year. On average it takes for invasive and fatal cervical cancer more than thirty yeas to develop and advance. On the other hand, due to

the current practice of regular Pap testing, cervical cancer death rate will continue to gradually decline by 4.2% per year with an expected cumulative number of lives saved of about 2,361 over 30 years.

The risk for human exposure to HPV will not be reduced by the HPV vaccines as both were designed to produce partial immunity against an extremely prevalent and usual infection. At least 120 HPV genotypes have already been identified and targeting just four in the vaccine may result in a limited coverage and inadequate protection. It is extremely complex and challenging for the healthcare and public health systems to make decisions regarding modern medical interventions such as the HPV vaccines, that seem to have unproven efficacy, questionable safety, and undetermined potentials; particularly if they are intended for use among otherwise healthy young individuals.

Regardless of vaccination, many other oncogenic HPV genotypes will continue to circulate unopposed and will continue to cause persistent infections. Every sexually active woman, including those properly vaccinated with *Gardasil* or *Cervarix* will continue to need regular Pap testing in order to detect pre-malignant lesions, and thereby prevent the development of cervical cancer. This research supports the fact that current population-based Papanicolaou (Pap) testing programs are proven efficacious in preventing cancerous and precancerous lesions of the uterine cervix. Death due to cervical cancer continues to occur because a significantly large number of females have no access to regular Pap smears, and/or other diagnostic tests. Providing easily accessible cervical cancer screening would also draw more underprivileged women into the healthcare system, which would have the added benefits of early detection and timely treatment of other diseases and conditions.

Females who get regular Pap tests almost never die of cervical cancer. Invasive cervical cancer is completely preventable and the death rate from it should be “zero” percent. If the risks associated with the HPV vaccine appear to be unremarkable, the immediate and long-term benefits are even more insignificant.

Although it is currently regarded as an inadequate vaccine, engineering *Gardasil* is a good start. Efficient or ideal HPV vaccines must cover all pathogenic (oncogenic and non-oncogenic) genotypes and should take in consideration the extremely high prevalence of the infection. Additionally, future vaccines should exhibit some therapeutic benefits for those who are already exposed and infected.

BACKGROUND

There is no doubt that cervical cancer prevention, early detection, and control are few of the public health success stories in the history of the fight against cancer. Since population-based screening programs utilizing Pap testing started to be widely implemented more than sixty years ago, cervical cancer incidence and deaths have declined more than 77% nationwide and continued to decline by a rate of 4.2% each year.[1] Pap smear is a cervical cancer screening test that identifies subtle cellular changes and can early detect premalignant and malignant cervical lesions. Abnormal Pap test findings are further evaluated for diagnosis and management.

Although it is one of the few preventable malignancies, each year cervical cancer continues to take the lives of about 3,400 American females and hundreds of thousands of women worldwide.[1] This is particularly disturbing because, theoretically, all precancerous lesions of the cervix should be avoidable through very effective primary

and secondary prevention strategies. Additionally, invasive cervical cancer should be easily preventable with a proper and regular screening and Pap testing, and the opportunities for numerous points of interventions during the very long latency period; about 30 years, it takes for invasive cervical cancer to develop and advance.[1] Furthermore, a very effective and relatively simple treatment is available to early-detected invasive cervical cancers or precancerous lesions with numerous opportunities for successful management during the long natural history of this disease.[2] Nevertheless; primary prevention is the ultimate goal for every disease control plan.

The identification of Human Papillomavirus (HPV) as the biological agent associated with cervical cancer provided a promising opportunity toward the achievement of this goal. Theoretically, preventing HPV infections should prevent cervical cancer. HPV is the most prevalent sexually transmitted infection in the United States (U.S.) and across the globe; more than 6.8 million Americans are newly infected each year.[3] The majority of HPV infections are unapparent, cause no clinical symptoms and are self-limiting. However, for a relatively small proportion of those individuals left untreated for persistent HPV infections due to certain oncogenic (cancer-associated) genotypes, there can be a slow and gradual progression to cervical displasia and cancer. The association between cervical cancer and oncogenic HPV genotypes is well documented in numerous studies, with a significantly high odds ratio (OR $\geq$ 15).[4] Additionally, infections with non-oncogenic HPV may lead to genital warts and could be associated with other vulvar, vaginal or anal dysplastic lesions and cancer.[4]

Two Human Papillomavirus (HPV) vaccines were recently licensed for use among teen-age girls and young adult females in the U.S. and the European Union,[5,6]

Gardasil, manufactured by Merck and Company Inc., and *Cervarix*, by Glaxo Smith Kline. Both are prophylactic vaccines; *Cervarix* is a bivalent vaccine that protects against two oncogenic HPV genotypes (16 and 18), while, *Gardasil* is a quadrivalent vaccine that protects against four genotypes; two oncogenic (16 and 18), and two non-oncogenic (6 and 11). Both vaccines require the completion of a three-dose series, starting with an initial intramuscular inoculation followed with a booster shot at one and six months.[5,6]

After approximately three years of population-based implementation, major questions have been raised as to whether these vaccines are effective in preventing cervical cancer as well as concerns about their safety, duration of protection, benefits, and cost-effectiveness.[7] Almost everything related to these two genetically engineered vaccines, that were designed to produce only partial immunity against an extremely prevalent infection, is currently under close examination. From the sound innovative theory behind engineering and the selection of HPV genotypes covered in the vaccine to the safety and purpose, these vaccines continue to be closely and carefully monitored.

According to the manufacturers, both genetically engineered vaccines, *Gardasil* and *Cervarix*, were originally developed to prevent cervical cancer,[8] yet tens of other HPV oncogenic genotypes were left uncovered by the vaccines, and unlike many modern vaccines neither one of them exhibits any therapeutic benefits against already existing HPV-related diseases or infections.[9] Therefore, regular life-long cervical cancer screening and Pap testing will continue to be very important and critically needed even for those who are properly vaccinated. Additionally, observed adverse events associated

with the administration of an HPV vaccine seem to be significantly higher than initially expected. [7]

In spite of many ongoing intense promotional and marketing campaigns targeting clinicians, policy makers, and public health officials, the lack of effectiveness data for these vaccines, as well as increasing concerns over their adverse events continue to hinder mass implementation, especially at the level of state cancer prevention programs.[10] It is extremely complex and challenging for the healthcare and public health systems to make decisions regarding drugs or vaccines such as *Gardasil* and *Cervarix* that seem to have unproven purpose and continue after three years of full implementation to exhibit undetermined disease prevention potentials, particularly if they are intended for use among otherwise healthy young individuals. Through an objective assessment of observed risks and benefits, this paper provides a thorough and objective review and evaluation of the HPV vaccine purpose, and assesses the value it may add to the commendable and sustainable efforts in the fight against cervical cancer.

VACCINE GENOTYPES

HPV is the most prevalent sexually transmitted infection. It is estimated that the life-time risk to contract this virus exceeds 90%.[3-6] According to the Centers for Disease Control and Prevention (CDC), more than 86% of all American females have already been infected with one or more HPV genotypes at some point in their lives. However, most of those women were able to clear the virus without any intervention and suffered no apparent short- or long-term negative health consequences. Most HPV infections are short lived and are not associated with displasia or cancer.[5]

Both *Gardasil* and *Cervarix* are genetically engineered and contain virus-like particles (VLPs) of the most predominant protein (L1) from HPV oncogenic types 16 and 18, implicated in causing cervical cancer.[11] Additionally, *Gardasil* covers non-oncogenic HPV types 6 and 11 believed to be associated with genital *condyloma accuminata* (genital warts). In its current format each of the vaccines leaves out more than 20 HPV oncogenic genotypes proven to be associated with cervical cancer and other genital malignancies, as well as more than a hundred HPV genotypes that could be responsible for genital warts and other HPV-related infections and diseases such as the *recurrent human papillomatosis* (laryngeal and respiratory polyposis).[10,11]

Studies that preceded the Food and Drug Administration (FDA) approval for *Gardasil* and *Cervarix* showed that about 70% of cervical cancers are probably associated with HPV genotypes 16 and 18.[11] However, it is unknown if such a finding played a role in the manufacturer's decision to limit the vaccine coverage only to these two oncogenic genotypes. Exact reasons for such selection and significant limitation in the vaccine coverage are unknown; continue to be vague and poorly explained by the manufacturer, unclear and probably unjustified to most healthcare providers and professionals. Leaving out at least twenty oncogenic and highly infectious pathologic HPV genotypes, no doubt, diminishes the vaccine's effectiveness.

Unfortunately, current medical knowledge regarding the effectiveness, safety, duration of protection, and ability of the HPV vaccines to prevent cervical cancer is limited and national data available after about three years of use is still incomplete and continues to be ambiguous. Meanwhile, it is logical and realistic to presume that in the absence of cross protection many other pathogenic HPV genotypes that are not covered

in the vaccine will continue to infect humans and could become even more dominant in causing HPV-related diseases.

The *Serotype/Genotype Replacement Phenomenon* observed with other vaccines is causing serous concerns among public health experts regarding to the HPV vaccines.[13] Eliminating just the two most dominant oncogenic HPV genotypes 16 and 18 through the use of *Gardasil* or *Cervarix* might allow for other HPV genotypes to emerge, become more aggressive, dominate and replace these two genotypes in causing dysplasia, thus reducing the effectiveness of the vaccine. Recent experiences with other vaccines such as *Prevnar* provide good reasons for such concerns. *Prevnar* provides selective and partial immunity to help protect younger children against the most prevalent seven strains of the pneumococcal bacteria that previously caused serious pneumonia and respiratory infections. However, after less than a decade of using *Prevnar,* several national studies and vaccine monitoring systems observed that children started to develop pneumonia due to more than 80 other pneumococcal bacterial strains that were not covered in *Prevnar*. Subsequently the manufacturers of *Prevnar* decided to enhance the vaccine by covering six additional strains of the pneumococcal bacteria. However, concerns continue that the serotype replacement process could be repeated even with the introduction of the new and improved *Prevnar 13*.

CLINICAL TRIALS

Since it was licensed for use in the U.S. on June 2006, *Gardasil* was explicitly promoted and marketed as the first vaccine ever invented to prevent cervical cancer.[5] A few days after the FDA-licensure, the Advisory Committee on Immunization Practices (ACIP) recommended *Gardasil* for routine vaccination among girls aged 11 to 12 years.[14] It was initially reported that *Gardasil* is very effective in reducing the prevalence of persisting HPV infections and dysplasia including cervical *intra epithelial neoplasia* (CIN) associated with one or both HPV genotypes 16 and 18.[15] However, a year after the FDA-licensure the manufacturer started, gradually, to release phase three clinical trial end-points (*i.e.,* CINII/III), and some study findings and outcomes that were not very encouraging. According to the Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE I) Study, the rates of mild to severe CIN (grades I to III), cervical neoplasia or adenocarcinoma in-situ per 100 subjects were 4.7 among vaccinated and 5.9 among unvaccinated.[15] This insignificant efficacy of about 20 percent was largely attributed to the reduction in CIN I incidence, with no observed effects on any higher grades of more advanced cervical displasia. Vaccinated subjects also exhibited lower rates of external anogenital and vaginal lesions (1.3 among vaccinated versus 2.1 in unvaccinated). In the more focused FUTURE II trial, rates of CIN II, CIN III and/or adenocarcinoma were 1.3 in vaccinated and 1.5 in unvaccinated women representing an efficacy of $\leq$ 17 percent which was unremarkable for CIN III or adenocarcinoma.[15] *Gardasil* was less effective when given to older females especially those already infected with HPV.

Most probably such low efficacy rates observed in FUTURE I and II trials were due to several reasons including:

- *Gardasil* was very effective in preventing infections due to HPV genotypes 16 and 18 covered in the vaccine. Nevertheless, most of the trial subjects (93%) were already sexually active, and less than 70% were naïve for both HPV genotypes 16 and 18. The risk of contacting HPV increases with age, number of sexual partners, and the early commencement of sexual activity. Existing HPV infections reduce the vaccine efficacy, therefore, the American Cancer Society (ACS) advised against vaccinating females who are older than 18, in spite of the CDC recommendation for a *Catch-up Vaccination Campaign* for females up to 26 years of age.[16]
- At least 20 additional oncogenic HPV genotypes have already been identified, and targeting just two in the vaccine may result in a limited and partial immune response that provides inadequate protection against the rest of the cancer associated genotypes.
- FUTURE II trial showed that the contribution of HPV genotypes, not covered in either of the vaccines, to the development of CIN I/II and adenocarcinoma was considerable. Additionally, the incidence of HPV genotypes 16 and 18-related infections and diseases among vaccinated subjects did not change, while the overall disease incidence rate, regardless of the HPV genotype, continued to increase over time. The complete elimination of the vaccine genotypes 16 and 18 may have created optimal conditions for other oncogenic HPV genotypes not covered in the vaccine to take over and replace the two suppressed genotypes. [11-15]

It is important to emphasize that long before publishing these humble results of clinical trials, vaccine manufacturers initiated massive promotional public and provider education campaigns highlighting the purpose of the vaccine to prevent cervical cancer. Such intense, focused, and persistent marketing approach targeted large numbers of healthcare professionals and policy makers, and probably influenced the critical analysis and could have biased objective decision-making.

Similar to other important drugs and vaccines that are urgently needed to prevent diseases and control infections and pandemics, *Gardasil* was fast tracked through the FDA system.[6] This process allowed *Gardasil* to be available to the public within six months of development. There were no newly emerging or reemerging public health threats coming from any HPV genotype nor any healthcare emergencies or any looming pandemic of cervical cancer. It is believed that the quadrivalent HPV vaccine was cleared too soon by FDA in-spit of the availability of Pap testing that is proven very effective in preventing cervical cancer.[8] A process that normally takes years from the initial application to the final approval was reduced to expedite the FDA licensure. [17]

In spite of an extensive worldwide ongoing marketing campaign, public health systems and leaders are uncertain regarding the new HPV vaccines. Although they are already in use, were endorsed by CDC, FDA, and ACIP who are currently collecting data regarding their safety, public health experts continue to have divided and conflicting opinions regarding their value in preventing morbidity and mortality, and improving the quality of life. Healthcare providers remain skeptical about the value of its widespread use, especially when effective well-established comprehensive cervical cancer screening programs and techniques are already in place in every state and almost every developed

country. Population-based cervical cancer screening programs are proven efficacious, cost-effective and are very successful in preventing and early detecting cervical neoplasia and cancer at an early and easily manageable stage.[18]

CERVICAL CANCER SCREENING AND THE HPV VACCINE

FUTURE II Study data showed that about 70% of the trial subjects were naïve for HPV genotypes 16 and 18, and demonstrated that about 70% of all cervical cancers are associated with these two genotypes already covered in the HPV vaccine.[15,18] Additionally it showed that *Gardasil* is effective in preventing infections due to HPV genotypes 16 and 18.

To evaluate the performance of the HPV vaccines we compared the number of lives that are saved due to regular cervical cancer screening with the number of lives that could be potentially saved due to the HPV vaccine. The most recent number of deaths due to cervical cancer (3,400) observed in 2009 in the U.S. was used as a baseline to compute the continuously compounding reduction in annual mortality due to each of these two interventions. The number of lives saved due to regular cervical cancer screening was calculated with the assumptions that the average annual rate of decline in cervical cancer mortality (4.2%) observed in the U.S. will continue to be unchanged. While, the number of lives that could be saved due to the HPV vaccine was estimated based on findings from clinical trials that lead to the FDA licensure for *Gardasil*, with the following assumptions:

- *Gardasil* is 100% effective in preventing HPV infections caused by genotypes 16 and 18.

- All females aged nine to 26 in the U.S. will receive and complete the HPV vaccine three-dose series in a timely manner.
- Up to 70% of all cervical cancers are associated with HPV vaccine genotypes 16 and/or 18.
- Up to 70% of all adolescent girls and young adult females who receive the vaccine are naïve to HPV genotypes 16 and 18.
- The protection of the vaccine would outlast the 30-year-long latency period for invasive cervical cancer. Undetected cervical cancer usually requires at least 30 years (latency period) to develop and advance resulting in death.
- It will take no less than thirty years for invasive cervical cancers to develop and kill the female host.

As presented in the table 1, it is projected that vaccination with *Gardasil* may have the potential to prevent up to 49% of cervical cancer deaths among those who were originally naïve for the vaccine genotypes 16 and 18 in the U.S. Subsequently, 30 years after vaccination, about 441 cervical cancer deaths that may occur due to persistent infections with HPV genotypes 16 and 18 can probably be prevented by the vaccine. On the other hand, due to the current practice of Pap testing, cervical cancer death rate will continue to gradually decline by 4.2% per year as represented in figure 1. It is projected that after 30 years of regular Pap testing, death due to cervical cancer will drop to 939/year. Subsequently, the cumulative number of lives that will be saved due to regular cervical cancer screening will be about 2,361 over the 30-year latency period.

Table 1. 30 Years of Projected Reduction in Cervical Cancer Death €

		Regular Cervical Cancer Screening				**HPV Vaccine**	
Year	Observed Number of Death§	Expected Number of Death	Observed % Reduction ₮	Expected % Reduction	Expected Number of Lives Saved*	Expected % Reduction¶	Expected Number of Lives Saved
2009	**3,400**	**3,400**	**4.2**	4.2	143	0	0
2010		3,257		4.2	137	0	0
2011		3,120		4.2	131	0	0
2012		2,989		4.2	126	0	0
2013		2,864		4.2	120	0	0
2014		2,744		4.2	115	0	0
2015		2,628		4.2	110	0	0
2016		2,518		4.2	106	0	0
2017		2,412		4.2	101	0	0
2018		2,311		4.2	97	0	0
2019		2,214		4.2	93	0	0
2020		2,121		4.2	89	0	0
2021		2,032		4.2	85	0	0
2022		1,946		4.2	82	0	0
2023		1,865		4.2	78	0	0
2024		1,786		4.2	75	0	0
2025		1,711		4.2	72	0	0
2026		1,639		4.2	69	0	0
2027		1,571		4.2	66	0	0
2028		1,505		4.2	63	0	0
2029		1,441		4.2	61	0	0
2030		1,381		4.2	58	0	0
2031		1,323		4.2	56	0	0
2032		1,267		4.2	53	0	0
2033		1,214		4.2	51	0	0
2034		1,163		4.2	49	0	0
2035		1,114		4.2	47	0	0
2036		1,067		4.2	45	0	0
2037		1,023		4.2	43	0	0
2038		980		4.2	41	0	0
2039		939		4.2	39	49	441
Total		**59,545**			**2,361**		**441**

€ 30 years is the average latency period for undetected and fatal cervical cancer to develop and advance
***** Expected number of lives saved each year due to regular Pap testing
¶ No cervical cancer death is expected among vaccinated females age nine to 26 before 30 years
§ Estimated number of annual death due to cervical cancer bases on latest estimations of the ACS
₮ Annual rate of reduction in cervical cancer mortality due to Pap testing is 4.2%

Even under the most favorable assumptions regarding its complete efficacy and duration of protection, the HPV vaccine would not be able to prevent any of the 30% of cervical cancers associated with many other HPV oncogenic genotypes not covered in the vaccine. Additionally, it would not help any of the 30% who were already infected with HPV genotypes 16 and/or 18 before getting the vaccine.

This comparison is intended to set the stage for future comprehensive long-term population-based studies to evaluate the effectiveness of the vaccine. However, it is important to underline that such a simple comparison is subject to some limitations including the following:

- The study assumed that up to 70% of those who will receive *Gardasil* are naïve to HPV genotypes 16 and 18. This assumption was based on findings from clinical trials that preceded the FDA-licensure for the vaccine. However, the effectiveness of *Gardasil* could be further reduced if this percentage turns out to be lower among the general population who could be substantially different that the trials' subjects.
- We assumed that every female aged nine to 26 will receive the vaccine. However, such assumption is impractical as currently about 33% of the females in the U.S. are not accessing regular cervical cancer screening, and probably they will not be able to access the vaccine.
- Not all females who will initiate the vaccine will be able complete the three-dose series. Furthermore, not all those who will complete the series will be able to do so in a timely manner which may further impact the effectiveness of the vaccine.
- Currently 70 % of all cervical cancers are associated with HPV genotypes 16 and 18. Eliminating these two genotypes by the vaccine may create a favorable climate for

other oncogenic genotype to become more aggressive or dominant which may further reduce the vaccine effectiveness.

- Our study assumed that the HPV vaccine will provide life long-lasting effective protection. However, the effectiveness of the vaccine could be further reduced if the duration of protection turns out to be shorter than the *latency period* (30 years) of cervical cancer.
- The annual rate of decline in cervical cancer mortality (4.2%) due to regular Pap testing practices observed in the U.S. over the past 14 years could change. It is expected that this rate will probably increase when more underserved females will be granted access to regular cervical cancer screening, especially after the implementation of the new universal healthcare reform.

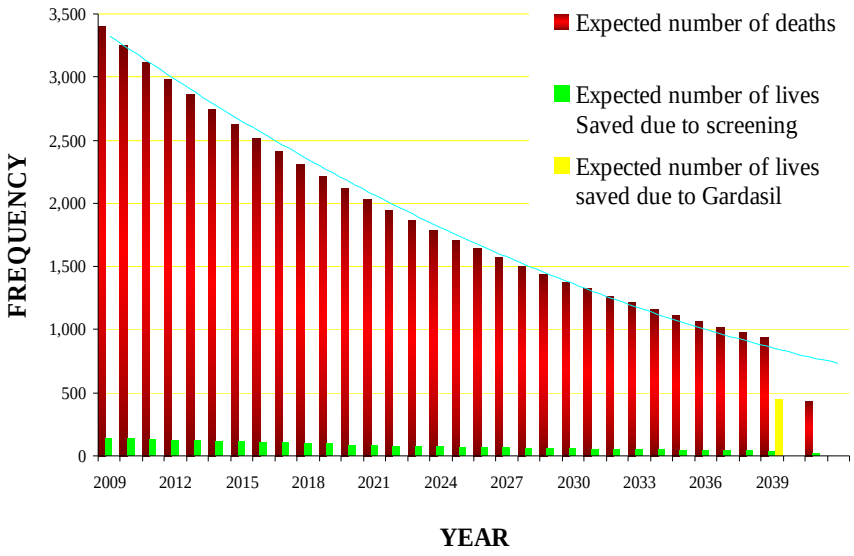

Figure 1. Projected Decline in Cervical Cancer Death
(U.S. 2009 to 2039)

ACCESS AND COSTE-FFECTIVENESS

Currently, the cost of the vaccine is a major obstacle to global deployment. *Gardasil* costs at least $585 for the complete course and *Cervarix* costs $560.[19] Additionally, the proper completion of the vaccine series requires three separate office visits, under the supervision of a licensed healthcare provider, in less than seven months. Due to such unfavorable circumstances, neither patients nor providers or insurance companies are eager to mass implement this novel costly medical intervention.

Several national and international research studies found *Gardasil* not to be a cost-effective intervention even under favorable assumptions regarding its complete safety and duration of protection.[20] The vaccine price would have to be decreased considerably, particularly that its effectiveness in preventing cervical cancer was never established. Currently, many healthcare providers continue to perceive such highly selective, narrow-focused vaccine as a complementary expensive tool that could have, in the future, some limited undetermined benefits for carefully pre-selected individuals. Additionally, the cost is a deterring factor for both the public health and healthcare systems and it further limits the public access to this expensive vaccine.[4]

Death due to cervical cancer continues to occur because a significantly large number of females have no access to regular Pap smears, and/or other diagnostic tests which detect pre-malignant growths and cancers in their earliest and most curable stages. The universal use of such tests would eliminate the need for expensive vaccines administered to otherwise healthy girls as young as nine years old. Providing free and easily accessible Pap tests would also draw more underprivileged women into the

healthcare system, which would have the added benefits of early detection and timely treatment of other diseases and conditions. Females who get regular Pap tests almost never die of cervical cancer. Invasive cervical cancer is completely preventable and the death rate from it should be “zero” percent.

Although cervical cancer death rate is relatively low and continues to decline, this currently observed rate is much far higher than it should be and reflects that Pap testing continues to be underutilized and not performed on at least 33% of American eligible women.[21] Such a finding is expected as more than 25.2 million females are currently uninsured and do not have regular access to preventive healthcare services or regular cervical cancer screening and Pap testing. Uninsured females, especially from underserved minorities and low-income families, who never access Pap testing, could probably have some potential benefit from *Gardasil* if it turns out to be effective and safe. However, such young females would be far better served by gaining access to the newly established comprehensive national healthcare system that should include preventive healthcare services and regular Pap testing to all eligible females in the nation. It is challenging to explain the strong FDA and CDC endorsement for new medical interventions with unproven benefits such as *Gardasil* versus the very little endorsement to extend the benefits of Pap tests to those who currently do not have access to preventive healthcare services.

It is universally agreed that every woman, even those properly vaccinated with *Gardasil* needs or will continue to need regular cervical cancer screening and gynecological exams, including Pap testing, in order to detect pre-malignant lesions, and thereby prevent the development of cervical cancer. Following standard regular screening

guidelines will probably further diminish the already unsubstantiated health benefits of the HPV vaccine, as it adds virtually nothing or a negligible value to the already successful fight against cervical cancer.

SUMMARY AND CONCLUSIONS

After this comprehensive review there continue to be several questions that could not be answered at the present time. Is this vaccine exposing women and teen-age girls to needless risks? How can public health experts and policymakers, as well, reach rational choices about the introduction of a new medical intervention? When do the benefits from a newly developed medical intervention outweigh the risks? When potential benefits such as in the case of HPV vaccines are undetermined or not obvious, many healthcare providers will be cautious to prescribe it and probably low numbers of females will be ready to accept the risks. At what level harmful adverse effects resulting from vaccines or any other medical intervention are considered excessive and when can we, epidemiologically, conclude that risks associated with a specific novel medical or surgical intervention may outweigh potential benefits?

Prudence is strongly recommended in view of many unanswered questions regarding effectiveness, duration of protection, safety and potential adverse effects that may emerge in future. Close monitoring of the vaccine performance and ongoing data collection regarding its short- and long-term impacts in order to guide informed public health best practices and decisions are definitely warranted. Extensive population-based long-term studies and research are needed.

More than a hundred of nononcogenic (low risk) and oncogenic (high risk) HPV types continue to be transmitted in an unopposed manner. Unfortunately, the risk for human exposure to such pathologens will not reduced by this vaccine. The prevalence of transient as well as persistent HPV infections among sexually active individuals is and will continue to be extremely high. The chance for humans to be exposed to or contract such infections (person-to-person transmission) could be inevitable especially among certain high risk groups. It is important to emphasize that the virus appears to be neither very virulent nor very harmful as almost all HPV infections are spontaneously cleared by the immune system. The exact relationship between infections at a young age and the development of cancer twenty to forty years later is still unclear and there is no practical and reliable way at the present time to differentiate between HPV infections that have the tendency to persist and progress and those that our body will be able to spontaneously clear.

Oncogenic HPV genotypes are necessary but insufficient carcinogens for cervical cancer. In addition to chronic persistent and progressive HPV infections, women with invasive cervical cancer usually lack access to regular Pap testing, have additional co-carcinogens including impaired body defenses and other behavioral risk factors such as smoking, multiple sexual partners, and inadequate nutritional status. [22]

Three years have passed since FDA licensed *Gardasil* and healthcare providers continue to be uncertain regarding the purpose or risks associated with the administration of this vaccine. Patients and parents need to understand their potential risks and benefits from HPV vaccination. Females who are sexually active should discuss with their

healthcare providers the value of regular cervical cancer screening and the options available should they choose not to be vaccinated.

How can policymakers make rational choices about the introduction of medical interventions that might do well in the future but for which evidence is currently insufficient? We may not know for many years whether such interventions will work or in the worst case do harm. Caution is needed in view of many unanswered questions and potential long-term adverse effects that may emerge in future.

Under the current safety profile the benefits of the vaccine, for an almost always harmless virus such as HPV, probably do not outweigh the risks or the rare adverse events for a perfectly healthy young girl. Current vaccines will not protect against HPV types to which women have already been exposed and it do not provide any cross protection against any other non HPV vaccine types. The selective ability of the vaccine to provide protection against only certain genotypes and eliminate just these four genotypes (6, 11, 16 and 18) may create a favorable setting and a niche for other pathologic HPV genotypes not covered by the vaccine to grow, dominate, and persist.

Undetected and never treated invasive cervical cancer takes decades ($\geq$ 28 years) to develop, advance and kill the host female. *Gardasil* is recommended for perfectly healthy young girls whose current risk for developing invasive cervical cancer is extremely low, and later in life such risks are even lower “negligible” and continue to decrease due to a very effective population-based screening practice. If the risks associated with the HPV vaccination appear to be unremarkable, the immediate and long-term benefits are even more insignificant.

According to CDC, the average age of females who died due to cervical cancer was ≥ 59 years, while the average age for adolescent girls and young adult females who died after HPV vaccination was 14 years and their median age was 15 year, demonstrating *years of potential life lost* (YPLL) that could exceed 75 per each girl.

Differences between *Gardasil* and popular childhood vaccines such as MMR (measles, mumps and rubella) are substantial. MMR was developed to prevent serious, acute, and highly infectious diseases with relatively high case-fatality rates. The benefits of vaccines such as MMR are evident and already established and validated through numerous long-term epidemiological studies in America and worldwide.[23]

It is debatable if parents of young children or healthcare providers would continue to accept such a relatively high rate of serious adverse events especially when similar or probably a better level of cancer prevention can be achieved with a regular Pap smear screening. Regardless of its potential to help prevent two HPV-related infections, *Gardasil* should never be administered without a prescreening for HPV because it may have the potential to worsen existing cases. It is highly recommended that girls be tested prior to their first inoculation for the presence of HPV in their system.

Although the number of fatal and other serious adverse events is not extremely high, such unfavorable outcomes are real and should be regularly monitored and thoroughly evaluated. Additionally, concerns are increasing that HPV vaccines may provide women with a false sense of protection. It is important to remember that the HPV vaccine will not eliminate the need for regular cervical cancer screening. However, public health experts are worried that it could result in a significant decrease in the rate of those

undergoing regular Pap tests, which in turn could contribute to an increase in cervical cancer.

The duration of the anti-HPV immunity provided by the vaccine is currently unknown. Long-term effectiveness of HPV vaccines is uncertain and may require booster shots later in life. Vaccine manufacturers acknowledge that the duration of immunity following immunization will only be determined after a substantial number of girls and young women have been vaccinated and followed for at least a decade.

Extreme caution is warranted in order to evaluate *Gardasil's* safety, efficacy, and duration of protection. Such evaluation should have been done before the implementation of population-based mass vaccination campaign.

Although it is frequently regarded as an inadequate vaccine, engineering *Gardasil* is a good start. An efficient HPV future vaccine should cover all pathogenic (oncogenic and non-oncogenic) HPV genotypes and should have some therapeutic benefits for those already infected. HPV is a sexually associated biological agent that is nearly universal in the human species, and genital infections with such extremely prevalent virus should be regarded as risk factors for dysplasia and cancer rather than as disease-causing. Just because a costly vaccine was recently developed to prevent two oncogenic out of more than a hundred twenty three genotypes of HPV does not justify mass vaccination for perfectly healthy girls and teenaged females.

Even if *Gardasil* and *Cervarix* turned out to be very safe and effective, these vaccinations are very costly and will not reduce the risk of exposure to or contracting HPV infections. Additionally, it will not reduce the need for routine life-long cervical cancer screening. Furthermore, it will not impact the incidence or death associated with

cervical cancer even if the protection against HPV genotypes included in the vaccine would outlast the decades-long latency period of invasive cervical cancer.

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CHAPTER 3

EVALUATION OF THE HUMAN PAPILLOMAVIRUS (HPV) VACCINE UTILIZATION IN NEVADA

ABSTRACT

The Food and Drug Administration (FDA) licensed the first human papillomavirus (HPV) recombinant vaccine, *Gardasil*, for general use among adolescent girls and young adult females in the United States (U.S.) in June 2006. Although millions of *Gardasil* doses were distributed, currently, it is unknown how many of those have already been used, who is prescribing it, and who is accessing this new vaccine. The characteristics of healthcare providers administering *Gardasil* and demographics of females who started or completed the vaccine series are not well described. This study focused on evaluating the characteristics of those enrolled in the Nevada Vaccines for Children (VFC) Program who received at least one dose of the HPV vaccine during the period between November 2006 and November 2009.

VFC Program database was electronically accessed and linked to other data systems from the State Department of Health. Additionally, data was cross-matched with the State Influenza Surveillance system to look for any history of influenza vaccination. Proportions of adolescent females, who started the HPV vaccine during the three-year study period, were calculated by age. Multivariate binomial regression was used to quantify and examine the impact of vaccine-related issues, client demographics, and provider characteristics on the initiation, compliance with the vaccine schedule, and completion of the three doses of the vaccine. Statistical analyses were stratified by five different age groups, and based on odds ratio (OR) estimates and associated P values subsets of measures from each category, such as adolescent's race/ethnicity and birth order, were selected for multivariable analysis.

Only a small percentage of the Nevada VFC Program enrollees started the vaccine series, and just a modest proportion of those were able to complete all three required doses. This evaluation revealed low levels of HPV vaccine orders among healthcare providers and decreasing demands among the program clients as well. As of November 2009, only 10,533 doses of *Gardasil* were used at all program providers' sites and most of those were administered in private offices. Records of 36,432 females nine to 18 years of age were identified and of those a relatively small number (6,965) received one or more doses of the HPV vaccine. More than 89% of those who started the vaccine did not complete the vaccine series, and only 40% of the adolescents who received the second dose completed all three doses.

Female's age and race/ethnicity were significant determinants for initiating and, to a lesser extent, complying with the vaccine schedule and completing the vaccine series. Compared to Caucasians, females of all other racial/ethnic groups demonstrated decreasing odds to start the series. African-Americans girls aged nine and 10, and those who were vaccinated by an internal medicine specialist, were least likely to start or comply with the vaccine schedule. Older age group Caucasian adolescents, girls who were seen at private medical offices and were vaccinated by a female pediatrician were more likely to start and complete all three required doses in a timely manner. A history of influenza vaccination was strongly associated with a higher likelihood of starting the HPV vaccine (OR = 1.28, 95% CI: 1.24, 1.33), receiving subsequent doses (OR = 1.13, 95% CI: 1.10, 1.15), and the completion of the vaccine series (OR = 1.41, 95% CI: 1.39, 1.44).

Gardasil is an extremely underutilized vaccine. Several noteworthy obstacles appear to negatively impact the vaccine utilization including a questionable safety record, unproven efficacy, especially when compared to regular cervical cancer screening, and an unfavorable public opinion due to ongoing extensive negative media reports.

Patient demographics and provider characteristics can strongly impact the utilization of *Gardasil.* Adolescent's age, race/ethnicity, history of receiving other vaccines, parental education level, clinic type; and provider's gender and specialty can significantly influence the initiation and completion of the vaccine series. In the absence of population-based studies on the safety, efficacy, and performance of *Gardasil*, this research provides an initial analysis and an up-to-date utilization review of this new vaccine.

BACKGROUND

The Food and Drug Administration (FDA) licensed the first human papillomavirus (HPV) recombinant vaccine, *Gardasil*, for general use among adolescent girls and young adult females in the United States in June 2006.[1] Since then millions of doses have been distributed in Nevada and nationwide. *Gardasil* is a genetically engineered quadrivalent vaccine that covers four HPV genotypes (6, 11, 16, and 18). It is injectable and requires three intramuscular doses to complete over a seven-month peiod,[2] and is it available for routine use among females age nine to 26 years.

Currently, it is unknown how many doses of *Gardasil* have been used, who is prescribing it, and who is accessing this new vaccine. The characteristics of healthcare

providers administering *Gardasil* and the demographics of the females who started or completed the vaccine series are not well described.

The Nevada State Vaccines for Children (VFC) Program provides nationally recommended vaccines at no charge to underserved, uninsured, and underinsured Nevada children. According to the Nevada State Department of Health and Human Services, the percentage of Nevada adolescents and children who do not have a medical home or regular access to preventive healthcare services ranges from 26.3 to 42.2 percent. Higher percentages are found primarily among children from underserved groups, low-income families and minority females, especially teenage girls of African-American or Hispanic origins. *Gardasil* became available in Nevada through the VFC Program in November 2006.

METHODS

To evaluate the HPV vaccine utilization, database from the Nevada Immunization Registry (NIR) and information from the VPD Program, in addition to other program-affiliated health plans, were accessed to identify records of program enrollees who were age and gender-eligible to receive the HPV vaccine during the study period. It was reasonable to assume that all adolescent girls in this study had similar opportunities to access the vaccine, and for the purposes of this research patient compliance with the vaccine schedule was defined as "receiving the second dose." FDA and other national public health organizations recommend the administration of the second dose in no less than 28 days and no more than 92 days after the first dose. FDA recommends no less than 12 weeks with no more than 27 weeks between the second and third dose. *Gardasil*

manufacturers strongly recommend the completion of all three doses in no more than six to seven months.[2]

Large sets of data from the Nevada State Health Division and other community health programs were analyzed. Statistical analyses were stratified by five different age groups. Multivariate binomial regression was used to examine and quantify how vaccine-related issues, client demographics, provider characteristics, and other healthcare or public health system-related issues had influenced the initiation of the vaccine series, compliance with the vaccine schedule, and completion of all three doses of the vaccine.

Using a unique identifying number for each subject, records were electronically linked and cross-matched with data from the Vital Statistics – Birth Certificate Program to ascertain age, race/ethnicity or to complete other missing information. Patients' records were also electronically linked to the State Influenza Surveillance System to look for any history of influenza vaccination including that for the monovalent novel H1N1 influenza virus vaccine.

The study protocol, methods and design were reviewed and approved by the Nevada State Department of Health and Human Services, the Centers for Disease Control and Prevention (CDC), and the Nevada Immunization Coalition. Data elements such as HPV vaccination site, date and dose (first, second or third), and history of receiving at least one flu shut during the study period (November 2006 – November 2009) were available from the electronic Immunization Registry records and the Influenza Surveillance System. Characteristics of healthcare providers and clinical sites where study subjects received the vaccine, including medical specialty and clinician's gender were extracted from the VFC Program database. Demographics for all study subjects including adolescent's

race/ethnicity, birth order, and mother's level of education, were available from the Client Enrollment Form to the VPD Program, and/or the Eligibility Form for the Bureau of Maternal and Child Health, as well as other databases available from the Division of Welfare.

In order to build a multivariate model and analyze patient and provider data we included variables from subjects' demographics, provider and site characteristics, and the influenza vaccination history. Selected measures from each subject included age, race/ethnicity, HPV vaccine dose, dose date, birth order, and mother's level of education were used to calculate crude and adjusted associations between the various demographic variables and the initiation of, compliance with the schedule, and completion of the HPV vaccination series.

The statistical analysis system (SAS) was used to perform data analysis for this research. Odds ratio (OR) were calculated. Additionally, we used the Poisson model with a robust error variance as an approximation in a few limited instances. Based on the odds ratio estimates and the associated P value for each variable, a subset of measures from each category that were mutually adjusted for other measures in the same category were selected for multivariable analysis. Multiple additional measures that were likely to represent other underlying factors were also used. Selection criteria was based on significant association in terms of a P value of < 0.05 and a magnitude of the point estimate of the odds ratio (e.g., OR ≥ 1.2).

STUDY FINDINGS

Records of 36,432 females nine to 18 years of age who met our study inclusion criteria by enrollment status, age, and gender were identified. Of those only 6,965 received one or more doses of the HPV vaccine. The proportion of adolescent females nine to 18 years of age enrolled in the VPD Program who started the HPV vaccine during the three-year study period is illustrated in figure 1. A relatively small percentage of the program enrollees started the HPV vaccine series and of those only one in nine (10.5%) completed the three required doses. In addition to several other factors, age and race/ethnicity of the adolescent females were highly significant determinants for initiating and to a lesser extent, completing the vaccine series.

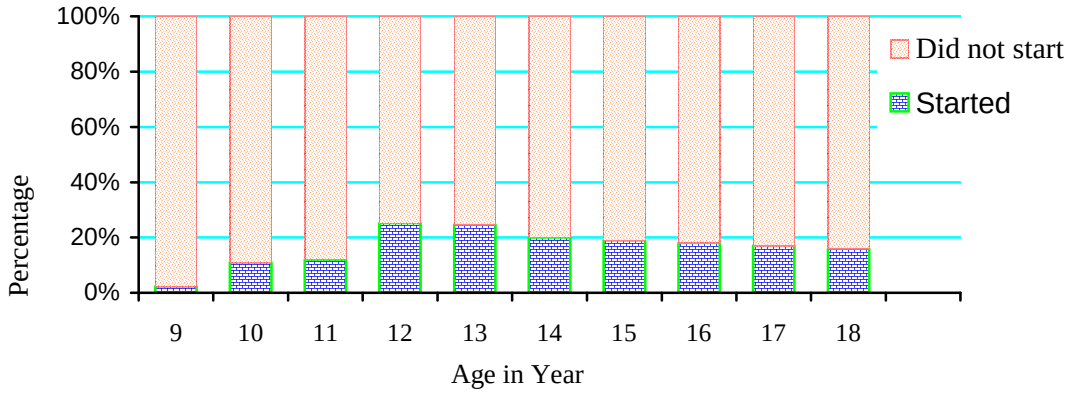

Figure 1. Proportion of Adolescent Females who Started the HPV Vaccine by Age (November 2006 and November 2009 – Nevada State Health Division)

Compared to Caucasians, girls of all other racial/ethnic groups in the study demonstrated decreasing odds to start the vaccine regardless of their age group. As represented in table 3, Asian/Pacific Islanders (OR = 0.25, 95% CI: 0.21, 0.34), girls whose race/ethnicity was coded as "other" (OR = 0.18, 95% CI: 0.15, 0.23), and African-Americans girls (OR = 0.33, 95% CI: 0.29, 0.41) were least likely to start the vaccine.

Furthermore, they were the least to comply with the vaccine schedule as represented in table 5, or complete the three-dose series as shown in table 6, especially young African-American girls who were vaccinated by a male internal medicine specialist at a community health clinic (table 5 and 6). Caucasian, older age group adolescent females were more likely to start the vaccine. However, Hispanic adolescents were most likely to comply with and complete the vaccination series, although this finding was statistically insignificant. Those who were seen at private medical offices (OR = 1.59, 95% CI: 1.53, 1.65), and girls who were vaccinated by a female pediatrician, were more likely to comply with the schedule and complete all three doses in a timely manner as illustrated in table 6.

HPV Vaccine

Nationally, *Gardasil* received immediate recommendation by the CDC's Advisory Committee on Immunization Practices (ACIP), and was strongly endorsed by the FDA for routine use against the virus that is believed to be associated with cervical cancer. However, *Gardasil* is not a required vaccine in Nevada. Currently, Nevada has one of the lowest childhood immunization rates in the nation[3,4,5] and consistent with that our study findings reflected low levels of HPV vaccine orders among healthcare providers and decreasing demands among VFC Program clients as well. As of November 2009, only 10,533 doses of *Gardasil* were used at all program-provider sites and most of those were administered in private offices. Between November 2006, and the beginning of 2007 the number of doses used by program providers at all sites steadily increased and peaked in the second half of 2007. That increase was more remarkable at private offices. However,

at the end of 2007 utilization started to gradually decrease and continued to decline through 2008. Utilization of the vaccine started to level off by mid 2008 in most of the VFC Program sites as is illustrated in figure 2.

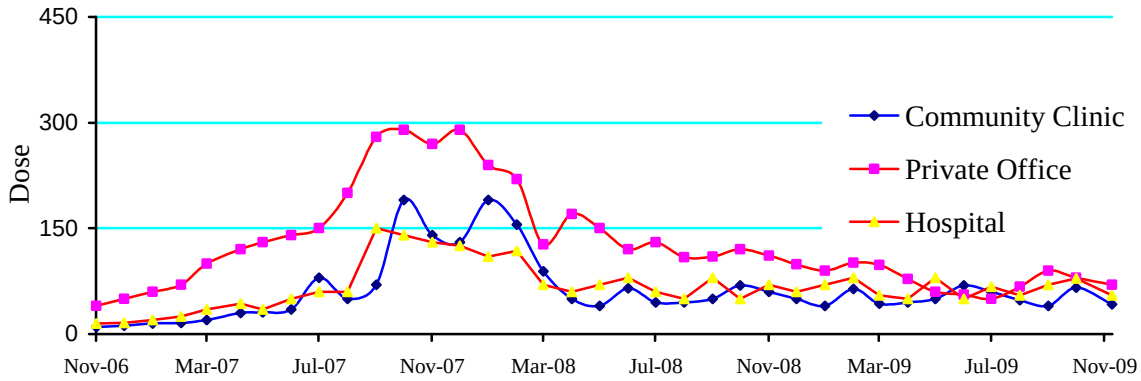

Figure 2. *Gardasil* Administered Doses by Provider Sites
(November 2006 and November 2009 – Nevada State Health Division)

Study Population

The Nevada VPD Program collects local and state level data on healthcare provider networks and program enrollees/clients and their families. It is nationally funded to provide childhood immunizations at no cost to underserved children especially from racial/ethnic minority groups who lack adequate access to preventive healthcare. Currently the program serves more than 171,114 Nevada children from low-income households. Although most of the program enrollees are underserved, it is widely believed that they are broadly representative of the diverse racial/ethnic, geographic distribution, and socioeconomic background of the state's population. Similar to several other states, the economy in Nevada continues to experience a major and prolonged economic recession. This sharp economic decline over the past few years resulted in unprecedented high rates of underserved, unemployed, uninsured, and underinsured

individuals and households becoming entirely dependent on public health services and state/federal programs to access healthcare. Records of 36,432 VFC Program females nine to 18 years of age who met our study inclusion criteria were analyzed. Of those less than one in five (6,965) received one or more doses of the HPV vaccine as illustrated in figure 3.

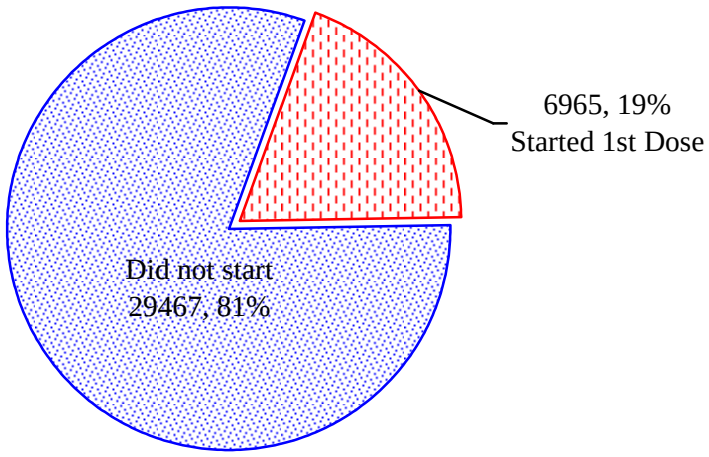

Figure 3. VFC Adolescents Who Received 1st Dose of *Gardasil*
(November 2006 and November 2009 – Nevada State Health Division)

According to the National Immunization Survey 25% of all adolescent girls aged 13 – 17 years in America had initiated the HPV vaccine series in 2007.[6] Although this study covered a three-year period (November 2006 - November 2009), the calculated annual average rate for vaccine initiation for the same age group was about 19%; suggesting a significantly lower percentage of HPV vaccine initiation among adolescent girls enrolled in the Nevada VPD Program. Additionally, of all adolescent females enrolled in the VPD Program who started the vaccine series during the study period only 1,834 or a little more than one in four (26.2%) complied with the second dose, and only 734 girls or one in nine (10.5%) completed all three required vaccination doses as illustrated in figure 4. It is

noteworthy that more than 89% of those who received their first dose did not complete the vaccine series, and only two out of five of those who received the second dose (40.0%) completed the series.

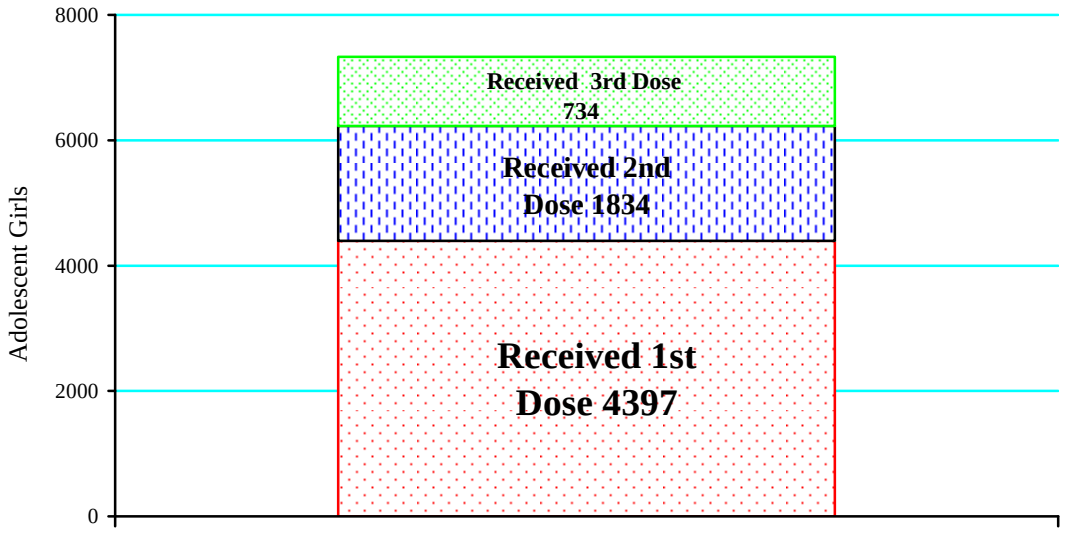

Figure 4. Compliance and Completeness of the HPV Vaccine Series
(November 2006 and November 2009 – Nevada State Health Division)

Many of those who completed all three doses did not comply with the vaccination time-frame suggested by the manufacturer. The median time observed in this study was 89 days between the first and second dose, with an extremely wide range of 14 to 528 days. While the median time between the second and third dose was 98 days with a range of 43 to 417 days as represented in table 1. Due to undocumented reasons a few of the girls received their subsequent doses earlier than recommended by the vaccine manufacturer. It is currently unknown what impact this could have on the vaccine efficacy and duration of protection.

Lack of compliance with the vaccine schedule was not due to a vaccine shortage. Healthcare providers regularly requested and received adequate supplies of the vaccine

from the state of Nevada, to cover all potential needs of program participants as illustrated in figure 5. Doses requested were comparable among the different clinical sites with private medical offices requesting the largest amount of the vaccine.

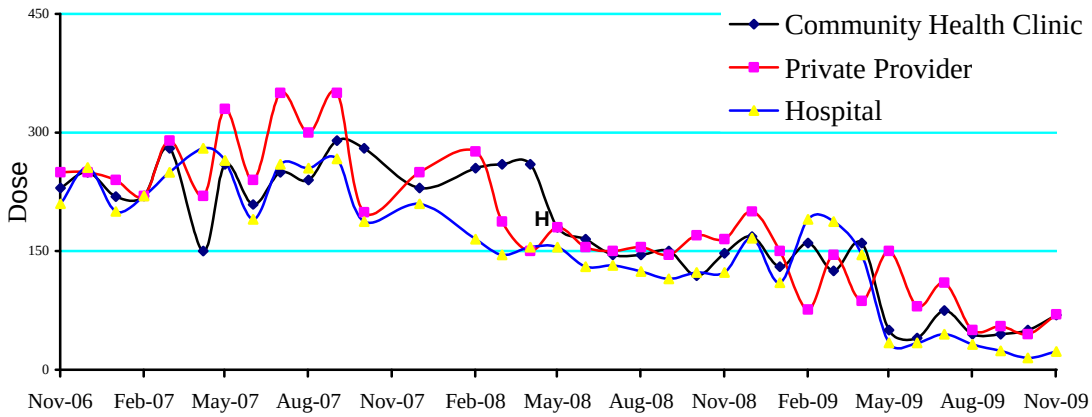

Figure 5. *Gardasil* Requested Doses by Provider Site
(November 2006 and November 2009 – Nevada State Health Division)

Table 1. Time Frame to Complete the HPV Vaccine Series (Nevada VFC Program 2009)

	Median	Range
Days between first and second doses	**89**	**14 to 528**
Days between second and third doses	**98**	**43 to 417**

Multivariate Analysis

A history of influenza vaccination was strongly associated with a higher likelihood of starting the HPV vaccine (OR = 1.28, 95% CI: 1.24, 1.33) as represented in table 3, receiving subsequent doses (OR = 1.13, 95% CI: 1.10, 1.15) as shown in table 5, and the completion of the vaccine series (OR = 1.41, 95% CI: 1.39, 1.44) as represented in

table 6. This finding suggests that compliant subjects who completed the HPV vaccine series tended to utilize other available preventive measures such as the influenza vaccine. Older age adolescents, Caucasian race, and being vaccinated by a female pediatrician at a private office, all correlated positively with higher odds for vaccine initiation and completion. Unexpectedly, education level of the adolescent's mother negatively correlated with initiating the vaccine (OR = 0.46, 95% CI: 0.41, 0.57) as represented in table 3. However once the vaccine series was started, the odds for an adolescent to receive the second dose (table 5), and complete the vaccine series increased among adolescents whose mothers were highly educated as represented in table 6.

Adolescent Characteristics

Findings from this post-FDA licensure study are primarily applicable for low-income adolescent girls enrolled in the Nevada State VPD Program "internal validity." However, some of the result specialty those provider-related could be generalized. Nevertheless, larger population-based studies are needed to ascertain "external validity." Based on the findings we can conclude that being part of a specific young age category (nine to 10 years old), or a certain racial/ethnic minority (e.g., African-American), and not having had a history of influenza vaccination (at least one flu shut) during the three-year study period were associated with a lower likelihood of HPV vaccine initiation, or complying with the vaccine schedule and completion of the vaccine series. Regardless of age and race ethnicity, having a male healthcare provider with a specialty in internal medicine and receiving the vaccine in a community health clinic were associated with lower odds for the adolescent females enrolled in Nevada VPD Program to complete the vaccine series.

On the other hand, having a female pediatrician as a healthcare provider, and a history of influenza vaccination, could be positive predictors for HPV vaccine initiation and completion even among females who are not enrolled in the program.

Once started the vaccine series, first born daughters were likely to comply with the schedule and complete the vaccine more than the second or third born. However, birth order was probably just a "confounding factor" that is more correlated to age than to the order of birth or family size (not included in data tables). Our study showed that third born daughters had the highest percentage (35.72%) to start the vaccination process as represented in table 3. Regardless of birth order; younger girls tended to follow the example of their older siblings. However, once started, first born daughters were more likely to comply with the vaccine schedule (OR = 1.47, 95% CI: 1.31, 1.67) as shown in table 5, and even better odds to complete the vaccine series (OR = 1.53, 95% CI: 1.43, 1.64) as represented in table 6. Such findings seemed to be more consistent with age-related factors in the study, as vaccination was more likely to be administered to older adolescent girls than to younger ones as represented in table 4. Additionally, such results are consistent with the national literature suggesting that providers were more likely to recommend the HPV and other STD-related interventions (i.e., Hepatitis B) to older adolescents.[7]

Compared to their Caucasian counterparts, young adolescents of African-American or Hispanic origin appeared to be underutilizing the vaccine. Previous market research studies reported that African-Americans, Hispanics, and Caucasian women had similar HPV vaccine acceptability. Therefore, it is unclear whether differences observed in our study were due to other factors not fully addressed in this research. Provider-and system-

related factors such as cultural sensitivity, vaccine availability, access to appropriate and competent preventive healthcare services, provider/patient ease of communication, and cultural attitudes toward HPV, as a sexually transmitted disease, have probably influenced the utilization of the vaccine.

Table 2. Determinants for Initiating/Completing the HPV Vaccine Series

	Least Likely to Start/Complete	**Most Likely to Start/Complete**
Race/Ethnicity	African-American	Caucasian
Age	9 and 10 years	17 and 18 years
Clinic Type	Community clinic	Private office
Provider Specialty	Internal medicine	Pediatrics
Provider Gender	Male	Female
History of Influenza Shot	No	Yes

It is important to emphasize that the growing controversy regarding the efficacy of this new vaccine, and its debatable safety record could have influenced the providers' behavior in recommending and administering this vaccine. While all of these factors are plausible, more studies are needed to understand the role of racial disparity in HPV- and other childhood vaccinations in order to identify root causes for these observed differences.[6,7]

The probability of contracting an HPV infection continues to increase after starting sexual activity. There is a baseline of about 11% increasing risk to contract an HPV infection shortly after starting sexual activity,[8] and the risk continues to increase at a rate

of about 11% with each additional sexual partner. More than 90% of all females in America become sexually active by age nineteen,[7] and more than one-third of those become infected with one or more HPV genotypes in their first year, and at least 50% contract the infection after four years of starting sexual activity.[7,8] However, it is important to emphasize that not all those exposed to HPV contract the infection and most of those who do are capable of spontaneously clearing the it without negative consequencies.[9]

HPV vaccine could be more effective if given before sexual debut, therefore we created an additional age group subset of data, for girls aged nine to 13 and compared those to older adolescent girls. Analyses were performed to further characterize and understand the age factor in influencing patients' decision to receive the vaccine, and providers' desire to administer it to older girls. Especially, because it is possible that higher proportions of younger girls have not started sexual activity yet. As represented in table 4 only 13.3% of the younger girls started the vaccination process versus about 29% of the older adolescent females in the program. The odds to start the vaccination process decreased with younger age (OR = 0.38, 95% CI: 0.35, 0.41), and again older age groups had higher chances/odds to receive the vaccine (table 4).

Provider characteristics

About 278 physicians practicing in 71 different clinics, and VPD Program-sites across Nevada are currently providing regular immunization services to the program clients. Immunization sites include 24 community health clinics, six hospitals, and 41 private medical offices. Adolescent girls under the care of a female pediatrician at a

private office were more likely to comply with the vaccine schedule and complete the three-dose series than those who were vaccinated by a male, internal medicine specialist or a clinician at a community health clinic. Such results were consistent with findings from our previous unpublished research that evaluated providers' knowledge, practices, and attitudes. Regardless of specialty, male healthcare providers appeared less likely than females to recommend the HPV vaccine. Such observations may reflect different provider interests in disease prevention patterns and the level of integrating the HPV vaccine into clinical practice by different clinical sites, specialties, or gender.

Our study results were consistent with findings from the National Survey of Family Physicians showing that female providers were more likely than their male counterparts to recommend the HPV vaccine.[10] However; alternative explanations other than physician attitude or gender are also plausible. For example, patient/provider comfort level in leading free and open communication about HPV mod of transmission, and the provider's approach to advising patients could play a role in a patient's decision-making process about vaccination. It is also important to mention that parental attitude may affect both the choice of healthcare provider's gender and specialty, and the decision for whether an adolescent daughter receives the HPV vaccine or not.[11]

DISCUSSION

In the absence of population-base studies, data and concrete results supporting the safety, efficacy, and performance of *Gardasil* at this time, our research provides an up-to-date thorough analysis and utilization review. It evaluates healthcare providers and the

public initiation of the vaccine, and measures compliance with the vaccine schedule and completion of the vaccine series.

Although most of the study's findings were consistent with other studies on childhood and adolescent vaccination, some of our research results were unexpectedly inconsistent with previously described patterns of positive, strong and well-documented correlation between the mother's education and the odds of her children initiating and timely completing their vaccinations. Previous research found that the higher the mother's education, the greater the chance that she will decide to vaccinate her children. Most of the studies reviewed indicated that parents who had graduate degrees were more likely to favor vaccination.[12] Our findings were probably influenced by the extent and importance of an informed parental decision and the decisive provider's recommendation for vaccination. Probably the ongoing controversy and increasing numbers of healthcare providers and parents who are questioning the efficacy and safety of *Gardasil* can provide some explanation. Such ongoing controversy may have contributed to highly educated parents rethinking their decision regarding *Gardasil*. On the other hand, it was observed (table 5) that the odds of compliance (OR = 1.31, 95% CI: 1.01, 1.69), and completion (OR = 1.40, 95% CI: 1.32, 1.58) of the vaccine among daughter of highly educated mothers, significantly increased after starting the series as represented in table 6. Such findings are consistent with previous studies and research reports regarding elevated rates of childhood vaccine completion observed among children of highly educated parents.[12]

Almost all studies and trials conducted to evaluate *Gardasil*, prior to FDA approval based their observations, analysis, and assessment on cohorts of subjects who volunteered

to comply with the proper vaccine schedule. Furthermore, healthcare providers and other clinicians who participated in such trials were probably well trained and precisely instructed on the proper use of the vaccine. This post-marketing utilization study focused mostly on underserved VPD Program clients and a subset of healthcare providers who provide services to such uninsured children in Nevada.

Compared to many other multi-dose injectable vaccines such as the Diphtheria, Tetanus, and acellular Pertussis (DTaP), Measles, Mumps, and Rubella (MMR), and the Hepatitis A and B vaccines, *Gardasil* demonstrated disappointing patient and provider compliance. Only a small percentage of the Nevada VFC/VPD Program enrollees started the series, and just a modest proportion of those were able to complete it. Furthermore, most of those who received two doses or more did not comply with the manufacturer's recommendations or time-frame to complete the series in less than seven months. However, it is essential to recognize that such a comparison may have several limitations. Although it is strongly recommended and endorsed by national organizations such as the CDC's Advisory Committee on Immunization Practices (ACIP), unlike DTaP or MMR, *Gardasil* it is not required for entry into school.

There are several noteworthy obstacles that appear to negatively impact the initiation, compliance with the schedule, and completing the vaccine series. In addition to a severe lack in healthcare coverage and very limited access to preventive healthcare services, especially in rural Nevada, provider-, patient-, and system-related factors seem to play major roles in reducing the utilization of this new vaccine. Individuals who chose to receive *Gardasil* and desire to have all three doses in a timely manner are required to have at least three medical office visits in a relatively short period of time. It is a

challenging task even for those who are fully covered under state public health plans to schedule more than one well-check office visit per year. Provider-specific factors for not complying with the vaccine schedule may include:

- Lack of proficiency and experience in prescribing and administering such a new multi-dose vaccine, coupled with an uncertainty regarding its performance, purpose, and value to replace or even complement regular cervical cancer screening.
- *Gardasil* lacks adequate protection against other HPV oncogenic genotypes that can cause cervical cancer.
- Many healthcare providers currently believe that the vaccine is not safe and they are hesitant to prescribe it to their patients unless and until they are sure that its benefits outweigh the risks.
- Currently there is no clear consensus on the HPV vaccine added value; especially in conjunction with regular cervical cancer screening.
- There are numerous provider-site related issues that could have contributed to such low rates of utilization and the modest provider/patient compliance, including:
    - Most of the provider sites in our study did not have adequate patient recall or reminder systems.
    - Most of the provider sites in this study demonstrated severe gaps in cultural competence, and only few offices had bilingual staff that was capable to provide informed consent or actively communicate with low-income, underserved teen-age minority girls.

Patient-related factors that could have led to such a low utilization and lack of compliance with the HPV vaccine series may include:

- Age-appropriate behaviors, consistent with a well documented lack of compliance with preventive healthcare services observed among teenagers.
- Unfavorable demographics for hard-to-reach individuals who reside in underserved rural and frontier Nevada counties.
- Socioeconomically deprived households and underprivileged children (*e.g.*, lack of reliable transportation, and/or baby-sitting) could have played a role in limiting the access to this vaccine.
- Unavailability of consistent healthcare coverage including temporary and unreliable insurance or limited coverage for preventive healthcare services.
- Unfavorable public opinion against *Gardasil* due to ongoing extensive negative media coverage. Cable News Network (CNN), Columbia Broadcast System (CBS) and several other national media outlets provided several documentaries and regular updates regarding increasing adverse events and deaths associated with the HPV vaccine.
- In the absence of prompt and assuring federal and state recommendations for mass immunization among girls and young women, public and private healthcare provides will continue to be undecided and confused regarding the value, feasibility, and safety of this new vaccine.
- Existing cervical cancer screening programs are currently providing comprehensive preventive healthcare services that are far-reaching beyond the simple detection of cervical cancer. Historically, such community-based programs were and still are the

only means for ever-growing large segments of underserved women across the nation to access preventive healthcare services. Additionally, cervical cancer screening programs continue to provide unique opportunities for many uninsured women to undergo regular annual check-ups as part of free comprehensive office visits. Such office visits usually include a physical exam and, as needed, laboratory work-up where other prevalent communicable and chronic diseases and conditions, including systemic illness such as diabetes, osteoporosis, heart disease, hypertension, or cancer are early detected and adequately treated.

Below expectation performance measures such as inability of many patients to comply with the schedule of this vaccine, may impact the immunological response leading to inadequate protection especially among those who failed to complete all three doses. Compared to regular cervical cancer screening, that is usually performed once a year, or every three to five years, proper immunization with *Gardasil* requires at least three office visits within a relatively short period of time. Challenges related to high costs, low levels of patient compliance with the vaccine schedule, and failure to complete the vaccine series in a timely manner, especially among young girls, could potentially impact the effectiveness of this vaccine and probably its duration of protection. Given the significant limitation, and difficulties facing *Gardasil* as a vaccine with no demonstrated benefits, it is unlikely that this new medical intervention will provide an adequate substitute for regular cervical cancer screening.

STUDY LIMITATIONS

There are several limitations to consider when interpreting the results of this study such as:

- The assumption that all adolescent girls enrolled in the VPD Program had similar opportunities to access the vaccine was not evaluated.
- All study subjects are underserved and have low socioeconomic status. Such demographics might have a different, more or less profound impact on starting the HPV vaccine among the general population or other underserved segments of the community that lack healthcare coverage and have no access to preventive healthcare.
- *Internal Validity*, our study findings are internally valid to the study population. However, several or our results need to evaluated for *External Validity.* The generalizability of the study findings outside the Nevada State VPD Program settings needs to be further assessed.
- Administrative data used in our study was not originally designed to serve research purposes and does not provide all medically relevant information.
- Databases and systems, as those used in the study, might not capture all vaccination events for each individual. A few of the program clients could have also been Medicaid recipients who could have been vaccinated outside the VPD Program sites.
- Electronic records that do not capture information on additional healthcare services delivered outside the Nevada VPD Program such as in those offered in free STD clinics or Planned Parenthood Clinics. It is also possible that teenagers

seeking counseling for family planning, oral contraceptive pills, or STD treatment may visit other types of providers and might have initiated the HPV vaccine or received subsequent doses elsewhere such as in urgent care centers, resulting in some degree of misclassification. Additionally, adolescent girls might also have access to the vaccine in other healthcare settings such as local county health departments or college and university student health centers. Although the magnitude of misclassification regarding the vaccine intake is unclear, it is likely that most of the vaccinated females would choose to receive the vaccine at a VPD Program site at no cost to them.

- Using available VPD Program administrative data, we were unable to evaluate the access to and availability of preventive healthcare services.
- There is a potential of underestimating the number of those who completed the vaccine series as our study did not capture compliance/completion of late starters. Additionally, there was a considerable backlog in data entry.
- This cross-sectional study analysis did not provide the opportunity to assess potential causal or temporal association between the lack of initiation, compliance with schedule and failure to complete the vaccine series with other access-related, and patient/provider-related reasons.
- Race/ethnicity data was lacking for a significant number of the subjects. To address this issue and reduce the gap, we cross-matched VPD Program data sets with the client enrollment database and other data available from the Nevada State Health Division, which resulted in reducing the missing data gap to about 6% of

the subjects. However, this approach could have resulted in underestimating confidence intervals.

- We combined race and ethnicity into one variable "race/ethnicity," thus we were unable to examine the association for Hispanic ethnicity separately from race. Therefore, further examination of the association between race and ethnicity and vaccine initiation and completion is warranted.
- Because of the relatively large sample size of those who qualified for the vaccine through the Nevada VFC Program, there could have been some associations that are statistically significant but clinically irrelevant. Our research did not focus on associations that were likely to be of clinical or healthcare nature.

Lastly, despite such potential limitations, our study exhibited several important strengths, including:

- A statistical study design that minimized selection bias.
- Through the use of electronic medical records versus self reporting data we avoided recall bias.
- Our public health research provides a sound approach to quantify, qualify, and evaluate in a near real-time approach the utilization of the new HPV vaccine, in spite of the ongoing controversy and uncertainty surrounding its efficacy, safety, duration of protection, and cost-effectiveness.
- Our statistical analysis was able to measure actual vaccine initiation and completion behaviors rather than relying on survey results to evaluate the intent to vaccinate.

- Large sample size of 36,432 adolescent teenage girls provided adequate power and confidence in the generated result.
- Findings from this study could be of value to public health professionals, healthcare providers, policy makers, the media and the public.

CONCLUSIONS

Relatively small proportions of teenage girls at the Nevada VPD Program started, complied with the HPV vaccine schedule and completed the vaccine series. Issues such as initiation, compliance, and completion of the vaccine schedule were not a challenge during any of the well-organized and highly structured clinical trials that evaluated vaccine effectiveness and led to the FDA licensure. Motivated trial subjects were carefully selected and specifically instructed to complete all three doses of the vaccine series as indicated. However, it is important to underline that the effectiveness of the vaccine was never evaluated among those who did not comply with the schedule and those who failed to receive all three doses appropriately and in a timely manner.

This up-to-date focused research, extensive statistical analysis, and descriptive study will assist healthcare professionals and community-based programs understand some of the potential obstacles to start and implement mass vaccination with *Gardasil*. Ongoing public education and greater awareness of programs and services available to underserved individuals and communities across the nation are important steps in the fight against cervical cancer. Three federal programs with the potential to reduce cervical cancer incidence, morbidity, and mortality are administered by the Centers for Disease Control and Prevention (CDC):

- National Breast and Cervical Cancer Early Detection Program (NBCCEDP)
- Vaccines for Children Program (VFC)
- Section 317 immunization grant program

These complementary programs provide education on the value of prevention, immunization, and screening/early detection services at no cost to underserved females who are most vulnerable for developing severe cervical displasia and dying from cervical cancer. All three programs are housed at the Nevada Bureau of Community Health.

Our study findings can provide some limited insight and an early look regarding public acceptance of this new vaccine and providers' attitudes toward *Gardasil;* especially that effectiveness, safety, and long-term efficacy of this vaccine are not yet established and continue to be evaluated. Probably there is a great need for more provider/public education, especially on the value of childhood vaccination. It is expected that information and findings from our study will be helpful for the healthcare system and for the policy makers to re-evaluate current public policy and refocus public health priorities on preventive healthcare services. Additional long-term studies are required to determine the vaccine effectiveness especially among those who did not comply with the vaccine schedule or did not complete the vaccine series.

Among all females in the US, uninsured, underinsured, economically disadvantaged, underserved, and minority women are at highest risk for developing invasive cervical cancer and dying from it.[13,14] Understanding the characteristics of those who obtained the vaccine versus those who did not may have important implications for future public health planning and policy making.

Based on current performance of several community-based cancer screening programs and findings from state and national studies, it is expected that females who are currently unable to access preventive healthcare services or are not compliant with existing established guidelines for regular cervical cancer screening will also have limited access to the HPV vaccine. Even when such females initiate the vaccine they might have difficulties in complying with the schedule or completing the vaccine series. It is unknown whether underserved teenagers who are not accessing and completing the HPV vaccine series exhibit similar behaviors toward other more important vaccines. Additional studies are also needed to evaluate providers' knowledge, practices, and attitudes towards vaccines in general in order to assess if our study findings are limited only to *Gardasil* or could also be also applicable to other more essential vaccines. This information is important to ascertain especially among providers who manifested low levels of participation and compliance.

Table 3. Starting the 1st Dose of *Gardasil* by Selected Adolescent Characteristics

Independent Variables (Adolescent Characteristics)	**Total**	**Started**		**Did not Start**		**OR**	**95% CI**	**P Value**
		N	**%**	**N**	**%**			
Race/Ethnicity								
African American	6,483	1,109	17.10	5,374	82.90	0.33	(0.29, 0.41)	<0.001
Caucasian	4,420	1,700	38.46	2,720	61.54	1.00	(ref)	
Asian/Pacific Islander	3,536	472	13.35	3,064	86.65	0.25	(0.21, 0.34)	<0.01
Hispanic	12,376	3,440	27.80	8,936	72.20	0.62	(0.51, 1.08)	0.19
Other	2,652	274	10.33	2,378	89.67	0.18	(0.15, 0.23)	<0.01
Adolescent Age in Years								
9 to 10	3,831	89	2.32	3,742	97.68	0.07	(0.2, 0.19)	<0.01
11 to 12	3,536	890	25.17	2,646	74.83	1.00	(ref)	
13 to14	5,304	1,846	34.81	3,458	65.19	1.59	(1.43, 1.64)	<0.01
15 to 16	8,251	2,067	25.05	6,184	74.95	0.99	(0.88, 1.13)	0.08
17 to18	8,545	2,103	24.61	6,442	75.39	0.97	(0.93, 1.1)	0.07
Birth Order								
First	9,429	2,765	29.32	6,664	70.68	0.75	(0.68, 84)	<0.001
Second	14,144	2,095	14.81	12,049	85.19	0.31	(0.21, 0.43)	<0.001
Third	5,893	2,105	35.72	3,788	64.28	1.00	(ref)	
Mother's Education								
Up to grade 12	22,984	5,285	22.99	17,699	77.01	1.00	(ref)	
Some college	4,715	1,466	31.09	3,249	68.91	1.51	(1.35,1.63)	<0.01
Graduate level	1,768	214	12.13	1,554	87.87	0.46	(0.41,0.57)	<0.01
History of Influenza Vaccination								
Received ≥ 1 Flu Shut	15,700	4,352	27.72	11,348	72.28	1.28	(1.24, 1.33	<0.001
Did not receive	13,767	2,643	19.20	11,124	80.80	1.00	(ref)	

Table 4. Starting the 1st Dose of *Gardasil* - Two Age Groups

Age at First Dose in years	**Total**	**Started**		**Did not Start**		**OR**	**95% CI**	**P Value**
		N	**%**	**N**	**%**			
9 to 12	7,367	979	13.3	6,388	86.71	0.38	(0.35, 0.41)	<0.001
13 to 17	13,555	3,913	28.9	9,642	71.13	1.00	(ref)	

Table 5. Compliance with the 2nd Dose of *Gardasil* by Selected Provider and Patient Characteristics

Independent Variables (Provider and Adolescent Characteristics)	**Total**	**Compliance with the 2nd Dose**		**Non-compliance with the 2nd Dose**		**OR**	**95% CI**	**P Value**
		N	**%**	**N**	**%**			
Site Type								
Hospital	1,855	505	27.2	1,350	72.76	1.38	(1.25,1.69)	<0.0001
Private Provider	3,290	940	28.6	2,350	71.43	1.47	(1.16,1.54)	<0.0001
Community Health Clinic	1,820	389	21.4	1,431	78.65	1.00	(ref)	
Provider Specialty								
General Practitioner	868	198	22.79	670	77.21	0.80	(0.70, 0.87)	<0.01
Pediatrician	5,875	1,580	26.89	4,295	73.11	1.00	(ref)	
Internal Medicine	53	12	22.47	41	77.53	0.75	(0.68, 0.77)	0.01
Other	169	45	26.35	124	73.65	0.97	(0.91, 1.02)	0.14
Provider Gender								
Female	4,501	1,209	26.86	3,292	73.14	1.00	(ref)	
Male	2,464	625	25.37	1,839	74.63	0.93	(0.86, 0.95)	<0.01
Adolescent Race/Ethnicity								
African-American	1,109	188	16.97	921	83.03	0.56	(0.43,0.61)	<0.001
Caucasian	1,700	457	26.87	1,243	73.13	1.00	(ref)	
Asian/Pacific Islander	472	89	18.84	383	81.16	0.63	(0.52,0.66)	<0.01
Hispanic	3,440	1,031	29.96	2,409	70.04	1.16	(0.98, 1.08)	0.19
Other	274	69	25.25	205	74.75	0.92	(0.80, 0.94)	<0.01
Adolescent Age in Years								
9 to 10	89	14	15.31	75	84.69	0.64	(0.62, 0.69)	
11 to 12	890	195	21.90	695	78.1	1.00	(ref)	<0.01
13 to14	1,846	481	26.06	1,365	73.94	1.26	(1.06, 1.43)	<0.01
15 to 16	2,067	548	26.52	1,519	73.48	1.29	(1.18, 1.56)	<0.01
17 to18	2,103	596	28.35	1,507	71.65	1.41	(1.19, 167)	<0.01
Adolescent Birth Order								
First	2,765	804	29.06	1,961	70.94	1.47	(1.31,1.67)	<0.001
Second	2,095	571	27.25	1,524	72.75	1.34	(1.15,1.50)	<0.001
Third	2,105	460	21.84	1,645	78.16	1.00	(ref)	
Mother's Education								
Up to grade 12	5,285	1,335	25.25	3,950	74.75	1.00	(ref)	
Some college	1,466	434	29.58	1,032	70.42	1.24	(1.09,1.39)	<0.01
Graduate level	214	66	30.69	149	69.31	1.31	(1.01,1.69)	<0.01
History of Influenza Vaccination								
Received ≥ 1 Flu Shut	4,352	1,203	27.64	3,149	72.36	1.13	(1.10, 1.15)	<0.0001
Did not receive	2,643	631	23.88	2,012	76.12	1.00	(ref	

Table 6. Compliance with the 3rd Dose of *Gardasil* by Selected Provider and Patient Characteristics

Independent Variables (Provider and Adolescent Characteristics)	**Total**	**Compliance with the 3rd Dose**		**Non-compliance with the 3rd Dose**		**OR**	**95% CI**	**P Value**
		N	**%**	**N**	**%**			
Provider Site								
Hospital	505	207	40.88	41	59.12	1.47	(1.45,1.59)	<0.0001
Private Office	940	403	42.87	537	57.13	1.59	(1.53,1.65)	<0.0001
Community Health Clinic	389	124	32.04	264	67.96	1.00	(ref)	
Provider Specialty								
Family Practice Islander	198	68	34.54	129	65.46	0.77	(0.73, 0.85)	<0.01
Pediatrics	1,580	644	40.76	936	59.24	1.00	(ref)	
Internal Medicine	12	4	34.06	8	65.94	0.75	(0.69, 0.79)	0.01
Other	45	18	39.94	27	60.06	0.97	(0.91, 1.02)	0.14
Provider Gender								
Female	1,209	493	40.79	716	59.21	1.00	(ref)	
Male	625	241	38.53	384	61.47	0.91	(0.86, 0.96)	<0.01
Adolescent Race/Ethnicity								
African American	188	47	25.10	141	74.9	0.51	(0.46,0.68)	<0.001
Caucasian	457	181	39.62	276	60.38	1.00	(ref)	
Asian/Pacific	89	25	27.78	64	72.22	0.59	(0.52,0.62)	<0.01
Hispanic	1,031	455	44.18	575	55.82	1.21	(0.98, 1.38)	0.19
Other	69	26	37.24	43	62.76	0.90	(0.80, 0.94)	<0.01
Adolescent Age in Years								
9 to 10	14	2	22.23	12	77.77	0.58	(0.53, 0.65)	<0.01
11 to 12	195	65	33.17	130	66.83	1.00	(ref)	
13 to14	481	190	39.47	291	60.53	1.31	(1.25, 1.44)	<0.01
15 to 16	548	220	40.17	328	59.83	1.35	(1.29, 1.47)	<0.01
17 to18	596	258	43.20	339	56.8	1.53	(1.45, 1.61)	<0.01
Adolescent Birth Order								
First	804	346	43.12	457	56.88	1.53	(1.43, 1.64)	<0.001
Second	571	236	41.27	335	58.73	1.42	(1.33,1.50)	<0.001
Third	460	152	33.08	308	66.92	1.00	(ref)	
Mother's Education								
Up to grade 12	1,335	510	38.18	825	61.82	1.00	(ref)	
Some college	434	194	44.72	240	55.28	1.31	(1.21,1.45)	<0.01
Graduate level	66	31	46.40	35	53.6	1.40	(1.32,1.58)	<0.01
History of Influenza Vaccination								
Received ≥ 1 Flu Shut	1,203	561	46.63	642	53.37	1.41	(1.39, 1.44)	<0.0001
Did not receive	631	173	27.42	458	72.58	1.00	(ref)	

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CHAPTER 4

EVALUATION OF SERIOUS ADVERSE HEALTH OUTCOMES ASSOCIATED WITH *GARDASIL*

ABSTRACT

Recently the Food and Drug Administration (FDA) licensed the first genetically engineered human papillomavirus (HPV) vaccine *Gardasil* for routine use among adolescent girls and young adult females in the United States (U.S.). Subsequently, and as with every new vaccine, post-licensure surveillance for adverse events was initiated. Shortly after the implementation of population-based vaccination programs, healthcare and public health systems in America and around the world started questioning the safety of this vaccine. This research evaluated selected serious adverse events reported to the national Vaccine Adverse Events System (VAERS) following vaccination with *Gardasil*.

Complex review and assessment of VAERS reports on negative health outcomes associated with *Gardasil* were performed on a weekly basis during the three-year study period (November 2006 to November 2009). Additionally, we conducted extensive data mining and analyses of several large data sets including historical data available from studies and clinical trials that lead to FDA licensure for the vaccine. Proportional reporting ratios and empirical geometric means were used to identify disproportionate reporting of adverse events to VAERS. To quantify the burden of serious unfavorable health outcomes, including deaths reported to VAERS after vaccination, we calculated rates per 100,000 distributed doses of the vaccine and compared those with background rates of serious illnesses, rate of death due to invasive cervical cancer, and rates of reported adverse events following vaccination with the meningococcal vaccine *Menactra*, and after vaccination with the monovalent novel H1N1 influenza virus vaccine.

We identified 15,829 VAERS reports of adverse events associated with *Gardasil*. Of those 1,289 (8.15%) were regarded as serious, including 49 deaths, 52 instances of

Guillain-Barré Syndrome (GBS), and 76 cases of blood coagulation disorders and intravascular accidents. The rate of serious and fatal adverse events reports following *Gardasil* was about 4.6 per 100,000 distributed doses. This rate was significantly higher than the rate of such events reported after *Menactra* (1.91 per 100,000), and after the monovalent H1N1 influenza vaccine (0.44 per 100,000). Additionally, compared to the average annual death rate resulting from invasive cervical cancer (3.1 per 100,000/females), there were no substantial differences between the risk of dying due to cervical cancer and the risk of developing severe and fatal health outcomes associated with the HPV vaccine.

No vaccine is 100% safe and effective. However, more than any other currently used vaccine, *Gardasil* was linked to higher incidence rates of serious adverse events, and compared to other vaccines the disproportional reporting of adverse events associated with *Gardasil* reflects significant differences that exceed expectations. However, the significance of this observation must be tempered with the limitations of a passive reporting system such as VAERS, and balanced with a well documented underreporting of adverse events following vaccination.

No causative relationship between receiving *Gardasil* and the observed adverse events has been established but we should take reports of temporal associations such as those demonstrated in this research very seriously. Although the number of fatal and other serious adverse events is not extremely high, such unfavorable outcomes are real. They should be regularly monitored and thoroughly evaluated. Under the current safety profile, it seems that the benefits of vaccination for an almost always harmless virus such as HPV do not outweigh the risks.

BACKGROUND

The Food and Drug Administration (FDA) licensed the first human papillomavirus (HPV) recombinant vaccine in the United States (U.S.) in June 2006.[1] The genetically engineered quadrivalent HPV vaccine *Gardasil* covers four HPV genotypes (6, 11, 16, and 18), and the bivalent vaccine *Cervarix* covers two HPV genotypes (16 and 18). Both are currently available for routine use among females aged nine to 26 years,[2] and both are injectable requiring three intramuscular doses to complete within a seven-month period.[2,3]

Ongoing vaccine safety monitoring is essential post FDA-licensure and the approval of new vaccines for population-based widespread use. As with every vaccine, the Centers for Disease Control and Prevention (CDC) and FDA are using VAERS to monitor *Gardasil*.[4] Post FDA-licensure surveillance for adverse events following vaccination with *Gardasil* was initiated in the second half of 2006, and for *Cervarix* in 2010. Post-marketing surveillance for new vaccines is essential to track long-term effects, and detect any potential short-term adverse events that were not identified or missed during the clinical trials that led to FDA approval.

After approximately three years of routine population-based utilization, the safety of *Gardasil* is increasingly questioned by the public health system, and state-based vaccine-preventable disease programs, and is repeatedly challenged by parents of young children, school nurses, and trial lawyers.

The main objective of our study was to evaluate serious adverse events associated with this novel vaccine in the United States. In order to accomplish that we thoroughly reviewed large numbers of reports on adverse events, assessed and analyzed large sets of

data, information, and reports submitted to VAERS in regard to *Gardasil*. Additionally, we analyzed complex historical data available from pre-licensure clinical trials in order to look for any subtle negative health outcomes that could have been missed or overlooked.

METHODS

During the three-year study period that started immediately after the FDA licensure for the HPV vaccine, VAERS reports were reviewed on a regular basis. We conducted extensive data mining, data validation and analysis; evaluated proportional reporting ratios and empirical geometric means to identify disproportionate reporting of adverse events. Medical records, hospital discharge data, laboratory reports, death certificate data, autopsy reports and several other data sources were electronically accessed and compiled. The statistical analysis system (SAS) and Epi-Info Version 3.5.1 were used to perform data analysis for this research.

To keep up with the rapid increase in reporting adverse events, VAERS data and reports were weekly evaluated. In order to quantify the burden of adverse events observed following vaccination with *Gardasil*, we calculated rates per 100,000 distributed doses of the vaccine and per person-years at risk, and compared those with background rates of serious illnesses such as Guillain-Barré Syndrome (GBS), death due to invasive cervical cancer, and reported adverse events following vaccination with other vaccines, such as the meningococcal disease vaccine *Menactra*, and the monovalent novel H1N1 influenza virus vaccine.

Although the number of distributed doses is available from CDC and the pharmaceutical companies, the exact number of vaccine doses that were administered is

unknown. In the absence of accurate numbers of those who already received the vaccine, numbers of distributed doses were used as surrogates to estimate that number.

Randomized clinical trials that preceded FDA-licensure for *Gardasil* focused mostly on the vaccine ability to prevent infections due to HPV genotypes 16 and 18 among those who were originally naive to these two oncogenic genotypes. Additionally, trial's data was, statistically, analyzed in one direction that evaluated benefits of the vaccine. However, our study analyzed historical data available from the same trials, but, in the opposite direction to look for any unidentified harms that could have been associated with the vaccine.

Pre-FDA Licensure Clinical Trials Data Analysis

To evaluate the effect of *Gardasil* on those who are already infected with HPV genotypes 16 and 18, we analyzed historical data sets available from the initial randomized double blind clinical trial that led to the FDA licensure for the vaccine. The trial 5,442 subjects already infected with HPV were divided into two comparable groups and randomized to receive *Gardasil* or a placebo. Laboratory samples collected prior to the administration of the first dose showed that 156 subjects in the *Vaccine Group* and 137 in the *Placebo Group* were already infected with the HPV vaccine genotypes *(PCR* positive and seropositive). No cervical dysplasia was detected among any of the trial subjects. However, at the conclusion of the study 31 subjects from the *Vaccine Group* and 19 from the *Placebo Group* manifested moderate to severe cervical intraepithelial neoplasia (CIN II/III) or worse as represented in table 1. The incidence rate of CIN II/III or worse was 11.1 per 100 person-years among those who received the vaccine, while it

was 7.7 per 100 person-years in the *Placebo Group*. Additionally, *Gardasil* exhibited no therapeutic effects among those who are already infected with HPV regardless of the genotype. It is unclear if the inoculation with *Gardasil* was associated with "accelerating" or "reactivating" the dysplastic process among those who had baseline evidence of persistent infections with HPV vaccine-genotypes. Appears that vaccination with *Gardasil* could have created the potential or circumstances for the HPV-related diseases to advance by 44.6% among those who were already infected with or carriers of the same HPV genotypes included in the vaccine. However, this increase was statistically insignificant and could have occurred due to chance only.

Table 1. Effects of HPV Vaccine on Trial Subjects with Evidence of HPV Infection with *Gardasil* HPV Genotypes

Endpoints	Vaccine Group N=2,717				Placebo Group N=2,725						
	N	cases	Person-Years at Risk	Incidence per 100 person-years	N	cases	Person-Years at Risk	Incidence per 100 person-years	RR	95% CI	P
≥ CINII/III due to HPV 6, 11,16, or 18	156	31	278.9	11.1	137	19	247.1	7.7	1.44	(0.74, 8.5)	0.21

Post-FDA Licensure Reporting of Vaccine Adverse Events

Healthcare providers as well as pharmaceutical companies are required to report to VAERS certain adverse events among vaccine recipients.[5] Additionally, members of the general public can report such events on a voluntarily basis.

Timely reporting allows for early detection of unexpected, newly emerging, rare, and potentially unusual patterns of short or long-term adverse events. Regular validation of VAERS reports and thorough ongoing evaluation of its findings can determine

whether an actual association exists between certain negative health outcomes and receiving a particular vaccine.[6] Furthermore, regular monitoring of reported adverse events and conducting cross-sectional epidemiological studies and analysis of VAERS data can provide accurate characterization of newly licensed vaccines.

Three national systems are currently in use to monitor post-FDA licensure vaccine safety:

1. The National Vaccine Adverse Event Reporting System (VAERS) serves as an early warning surveillance tool to assist CDC and FDA in detecting unexpected side effects or other emerging adverse events following vaccination.[7]
2. The Vaccine Safety Datalink (VSD) Project is a comprehensive collaborative effort between the Immunization Safety Office at CDC and eight large managed healthcare organizations (MCOs) to address existing gaps in scientific knowledge regarding infrequent but serious events following immunization.[8]
3. The Clinical Immunization Safety Assessment (CISA) Network is a national network of six medical research centers conducting clinical research on immunization associated health risks. [9]

VAERS adverse events include health problems that were reported after vaccination, regardless whether they were related to the vaccine or not. Such negative health outcomes may or may not have been caused by the vaccine. Some of these events may occur coincidentally, during the time period following vaccination, while others may actually be caused by vaccination. For the purposes of our research negative health outcomes reported to VAERS were classified as:

a. Serious Adverse Events[10] including persistent and/or progressive illnesses and conditions that follow vaccination. Such events usually lead to prolonged hospitalization and may include chronic debilitating life-threatening illnesses, permanent disability, and eventually death. Serious adverse events reported to VAERS are regularly assigned to predetermined broad diagnostic categories and are reviewed by experts from CDC and FDA. To verify and validate all serious events, CDC usually requests medical records for conditions that are consistent with anaphylactic shock, neurological impairments, coagulation disorders, Guillain-Barré Syndrome (GBS), or death.
b. Non-serious Adverse Events usually involve non-life-threatening negative health outcomes that are more frequently encountered following injectable vaccines including fainting, pain, headache, nausea, fever, and inflammation or swelling at the injection site. [10]

STUDY FINDINGS

The first doses of the quadrivalent HPV Vaccine *Gardasil* became available for general use in the second half of 2006, and during the three-year study period (November 2006 to November 2009), there were approximately 28 million *Gardasil* doses distributed in the U.S. We identified 15,829 VAERS reports of adverse events associated with *Gardasil*. Of those only 1,289 (8.15%) were regarded as serious or fatal, including 49 deaths, 52 instances of Guillain-Barré Syndrome (GBS), and 76 cases of blood coagulation disorders and intravascular accidents. However, the vast majority of these adverse events (14,540 or 91.86%) were defined as non-serious including fainting, injection site pain, headache, nausea, and fever.

About 50% (7,912) of all adverse events following *Gardasil* occurred on the same day of vaccination, and more than 13% (2,068) were due to syncope. This rate is comparable to what is usually observed with other injectable vaccines given to adolescent girls.[11] However; it is remarkable that about 42% of the adolescents' syncope cases observed after *Gardasil* were associated with additional disturbing clinical manifestations such as deep loss of conscious, knee jerking, tonic/clonic movements, loss of bladder control, *grand mal* seizures and other seizure-like activities. Furthermore, 93% of these clinical signs occurred within 15 minutes of vaccination.

The computed rate of serious and fatal adverse events reports following *Gardasil* was about 4.6 per 100,000 distributed doses. It was higher than the rate of such events reported after *Menactra* about 1.91 per 100,000 (RR = 2.4, 95% CI: 0.44, 13.01), or after the H1N1 influenza vaccine about 0.44 per 100,000 (RR = 10.4, 95% CI: 0.47, 230.04). Additionally, compared to the average annual death rate resulting from invasive cervical cancer (3.1 per 100,000), there were no substantial differences between the risk of dying due to cervical cancer and the risk of developing severe and fatal health outcomes associated with the HPV vaccine. However, assuming that all those who started the vaccine were able to complete all three recommended doses, this rate could be as high as 13.8 per 100,000 vaccinated females. Subsequently, the relative risk for those who receive the quadrivalent vaccine series was about four times (RR = 4.45, 95% CI: 1.29, 15.26), significantly higher than the risk of death from invasive cervical cancer ($P < 0.01$).

It is extremely complex to infer causal relationships between a newly developed vaccine and negative health outcomes reported to VAERS; especially that many of the serious events are subtle, insidious, and may not be reported. Such a comparison is primarily intended to set the stage for more highly structured long-term studies that would evaluate the vaccine risks/benefits, effectiveness, and duration of immunity.

Deaths

We identified 49 reports of death among adolescent girls and young adult females in the United States who received *Gardasil* before December 2009. However, only 28 of those were verified and confirmed by CDC, while the other 21 fatal events had incomplete documentation and were pending additional follow-up and investigations. Nevertheless, associations with *Gardasil*, underlying cause/s of death, and clinical diagnoses for each of these 49 death events were ascertained from medical records, death certificates, and autopsy reports for events where autopsies were performed.

There was no obvious common cause or unique pattern to cluster these fatal cases or to suggest that they were the result of HPV vaccination. Several of the fatal cases could be explained by factors other than the vaccine. Underlying causes of death included diabetes mellitus, viral infections, anaphylaxis, illicit drug use, cerebrovascular accidents, and heart failure. However, one or more significant underlying causes including disease entities that could have been associated with HPV vaccination, such as coagulation disorders and anaphylactic shock, were identified in 39 (80%) of the deceased case reports. Three autopsy reports described unusual neurological illnesses that were consistent with or comparable to the *Amyotrophic Lateral Sclerosis* (ALS) often

referred to as "Lou Gehrig's" Disease that resulted in death in all three young females. Death reports associated with *Gardasil* reflected a range of underlying conditions; some can be reasonably attributed to the HPV vaccine, while others could be related to pre-existing medical, immunological, or neurological chronic conditions.

The median age of death was 15 years and that is consistent with the age of the vaccine target-population. Following vaccination with *Gardasil*, death occurred after variable periods of time that ranged from 43 minutes to more than a year and seven months, with a median of ≤ 4 days. Twenty-nine deaths occurred less than a week after vaccination and 20 of those occurred in less than four days. No specific pattern related to patient's demographics (*e.g.,* race/ethnicity, geographic location, insurance, and education), or other characteristics that could be provider-related (*e.g.,* medical specialty, or clinical site) were observed.

According to CDC and FDA, there is no currently compelling evidence to suggest that the HPV vaccine caused any of these fatal illnesses. Nonetheless, researchers from several highly regarded academic centers are carefully examining the circumstances and the evidence surrounding each fatal case and are evaluating potential linkages between vaccination with *Gardasil* and any subsequent fatal illnesses. Tissue samples from several of the fatal cases have been submitted to CDC for laboratory studies and further characterization.

The remaining 1,240 nonfatal cases that manifested serious adverse events associated with the HPV vaccine as represented in table 2 continue to be under close CDC and FDA observation. Such cases fall into the diagnostic category of serious

neurological impairments, vascular accidents, and muscular dystrophies. Other adverse event reports submitted to VAERS as of November 30, 2009 are summarized in table 3.

Table 2. Frequency of Reports on Serious/Fatal Adverse Events Associated with *Gardasil*

Optic Neuritis and Blindness	**16**
Nephritis	**20**
Heart Failure	**88**
Paralysis	**84**
MS	**21**
Thyroiditis	**7**
Death	**49**
Steven-Johnson Syndrome	**5**
Systemic Lupus	**12**
Anaphylactic shock	**109**
Clotting disorders	**76**
Guillain-Barre Syndrome	**52**
Transverse myelitis	**57**
Pancreatitis	**21**
Lung infarction	**37**
Grand mal Seizures	**313**
Motor neutron lesions	**311**
Amyotrophic Lateral Sclerosis	**11**
Total	**1,289**

Although death events that occurred during or after receiving *Gardasil* manifested no clear patterns to suggest or infer causality, healthcare providers worldwide are increasingly questioning the safety of the HPV vaccine and demanding close monitoring with more extensive population-based studies.

It is noteworthy to highlight that since the conclusion of our study additional deaths associated with *Gardasil* continued to occur, and each one of those was ascertained from the individual death certificate. Recently CDC confirmed additional 25 deaths raising the official number of CDC-confirmed deaths associated with *Gardasil* to 53.[12] None of those new cases is included in our study.

Guillain-Barré Syndrome (GBS)

Guillain-Barré Syndrome (GBS) is a rare neurological disorder that may lead to a gradual progressive ascending muscular weakness. Under usual circumstances, less than two per 100,000 teen-age girls are expected to develop this disorder. It is usually observed following serious, debilitating, acute or chronic persistent infections. It is worthwhile mentioning that GBS was reported after vaccination with *Gardasil* during the pre-licensure clinical trials; however, there was no evidence that HPV vaccination increased the incidence rate of this serious illness among trial subjects.

As of November 30, 2009, we identified and confirmed 52 GBS cases reported to VAERS following vaccination with *Gardasil*. Forty-two cases (80.7%) of those developed the disease around six weeks after vaccination, 38 were younger than 19 years, and 14 were 20 to 26 years old. Thirty-two cases (61.5%) received no other vaccines during that period, while 20 females (38.5%) received flu shots and/or the meningococcal vaccine *Menactra* along with *Gardasil*.

The frequency of GBS cases associated with HPV vaccination appeared to be slightly higher than expected. However, that increase was statistically insignificant. Nevertheless, most of these cases were clustered in time within six weeks after

vaccination. Such observations may warrant more careful monitoring of the GBS occurrence among HPV vaccine recipients for case ascertainment and to conduct additional health evaluations. Future epidemiological studies could add more insight, meaning, and explanation for this noteworthy temporal distribution among cases.

Clotting and Coagulation Disorders

During the three-year study period, 76 reports of serious adverse intravascular coagulation events were observed after vaccination with *Gardasil*. Clotting disorders involved coronary arteries, central nervous system, pulmonary vessels, renal arteries and lower extremities. Many adolescents manifested ischemic heart disease (IHD), cerebrovascular disorders (*e.g.,* stroke, and seizures), pulmonary embolism, renal, and lung infarctions. Additionally, deep venous thrombosis (DVT) events were observed after the vaccine.

According to recent CDC data reports, most of the females who manifested such disorders had additional co-morbidities and risk such as being on oral contraceptive pills, tobacco smoking, overweight or obesity, and having had other significant behavioral risk factors such as unhealthy nutrition and physical inactivity. Similar to other serious adverse events associated with *Gardasil,* the frequency of reporting pulmonary embolism, DVT and other coagulation disorders, observed after receiving the vaccine was relatively high compared to other vaccines that are frequently administered to teenage females. However, this observed increase was statistically insignificant.

Gardasil and the Novel Influenza H1N1 Vaccine

The FDA-licensing process for the monovalent H1N1 novel influenza virus vaccine was accelerated during the fall of 2009 in order to counteract and control the rapid spread of the newly emerging H1N1 influenza virus. [13] School-age children and young adults were among the five high priority groups identified by CDC to receive the vaccine.[14] As of November 30, 2009, there were more than 43 million distributed doses of the vaccine, and during our study period (November 2006 – November 2009); there were about 28 million doses of the HPV vaccine *Gardasil* distributed in the United States. The overall VAERS adverse events reporting rate was 56.3 per 100,000 distributed HPV vaccine doses compared to 8.2 per 100,000 distributed doses of the H1N1 novel influenza vaccine.[15] Additionally, the reporting rate of serious and fatal adverse events associated with the HPV vaccine was 4.6 per 100,000 distributed doses compared to less than 0.44 per 100,000 distributed doses of the H1N1 novel influenza vaccine. The rate of serious adverse events reported after *Gardasil* was more than ten times higher than that after the novel H1N1 influenza virus vaccine. Although the apparently elevated rate of serious adverse events reported to VAERS after vaccination with *Gardasil* was statistically insignificant, the difference between rates of serious adverse events reported after the novel H1N1 influenza virus vaccine and after the HPV vaccination was significant (P Value $\leq$ 0.0041). For each adverse event reported after the novel H1N1 influenza virus vaccine there were more than six reports submitted to VAERS after vaccination with *Gardasil*.

Gardasil* and *Menactra

During the comparison between adverse events reporting rates following *Gardasil* and *Menactra*, we observed patterns that are similar to those observed in the comparison between *Gardasil* and the Novel H1N1 Influenza Virus Vaccine, but, to lesser extent. Analysis of the frequency and severity of adverse events reported to VAERS through November 30, 2009, reveals that death and serious negative health outcomes such as GBS, stroke, blood clots, cardiac arrest, seizures, and even fainting, were reported three to 30 times more frequently following *Gardasil* than after *Menactra*.

Both *Gardasil* and *Menactra* received FDA licensure within a year of each other and both were recommended by CDC for universal use among children 11-12 years of age. *Menactra* is administered to both genders and was mandated in several states for high school and college entry.[16] It is administered as a one-dose series, and by February 2008, CDC records showed that 15.5 million doses of *Menactra* had been distributed in the U.S. As of that date there were 26 confirmed case reports of GBS that developed less than six weeks following vaccination with *Menactra*. Twenty-four of those were among children 11 to 19 years old and two were among young adults 20 years and older. Such findings may suggest a slight increase in the rate of GBS among *Menactra* recipients (0.17/100,000). However, according to CDC experts such findings should be viewed with caution.[17]

Based only on the number of observed cases, this rate is similar to what might have been expected to occur by chance alone. However, the temporal distribution of cases and the onset of neurological symptoms associated with GBS (two to 32 days)

following vaccination is probably a cause for concern. Several epidemiological studies are ongoing at CDC to further evaluate this observation. The precise rate of GBS among adolescents in the United States is unknown. Data from the Vaccine Safety Datalink Project and the Health Care Utilization Project on GBS incidence among persons aged 11 to 19 years showed a background annual incidence of 1 to 2 cases per 100,000 person-years.[18] Nevertheless, as part of the consent form for receiving the *Menactra* vaccine, CDC recently issued a strong warning and recommended that adolescents and their caregivers be informed about these adverse events and the ongoing follow-up studies. Additionally, CDC alerted healthcare providers not to vaccinate individuals at high risk for seizures and those with a history of GBS who are not in a high-risk group for invasive meningococcal disease.[19]

On the other hand *Gardasil* is not a mandatory vaccine and it was licensed only for use among teenage girls and young adult females to prevent infections with four HPV genotypes that could be associated with about 70% of cervical cancers. *Gardasil* is given in a three-dose series and by July 2008 there had been about 16 million doses distributed in the U.S. Assuming that females who initiated the vaccine were able to complete the recommended three-dose series, such an amount could have been adequate to immunize more than five million females. Analysis of VAERS reports as of that date identified 38 confirmed cases of GBS that developed in less than six weeks following vaccination with *Gardasil*. Twenty nine of those were younger than 19 years and nine cases were 20 to 26 years old. Similar to the observation of GBS cases associated with *Menactra* such finding may suggest a slight increase in the rate of GBS among *Gardasil* recipients (0.24/100,000). Evidently, due to some limitations, this finding should be viewed with

caution. Additionally, based only on the number of reported cases this rate is similar to what might have been expected to occur due to chance alone. However, in spite of several data limitations and the statistically insignificant increased risk of GBS following vaccination with either one of the two vaccines, the relative risk (RR = 1.41, 95% CI: 1.27, 1.49) for a teenaged female to develop GBS after receiving *Gardasil* was 40% significantly higher than after receiving *Menactra* ($P < 0.05$).

VAERS reports were also used to identify the scope and severity of selected adverse events associated with *Menactra or Gardasil* vaccination. Regardless of the nature of illness, death and other serious adverse events, including clotting disorders, were three to 30 times more frequently reported after *Gardasil* than after *Menactra*. It is also important to underscore that compared to females who received only *Menactra* the relative risk was slightly but insignificantly increased for those who received both vaccines concomitantly.

Gardasil and Cervical Cancer Death

No substantial differences were observed between the risk of dying due to cervical cancer and the risk of developing serious and fatal adverse events associated with HPV vaccination. Assuming that all those who received *Gardasil* completed the vaccine three-dose series, the estimated rate of reported serious and fatal adverse events associated with HPV vaccination in the U.S. could be as high as 13.8 per 100,000 vaccinated females. The risk for those who receive the quadrivalent vaccine *Gardasil* series to develop serious and fatal adverse health outcomes after vaccination is currently four times significantly higher than the risk of death due to invasive cervical cancer. Such

an unexpected and disturbing finding should set the stage for more extensive monitoring and evaluation studies; especially that the declared purpose of the vaccine is to prevent cervical cancer itself.

Even when causal relations between the HPV vaccine and severe or fatal adverse events are not established, it is important to emphasize that the natural history of cervical cancer is very long and the average number of years it takes for an HPV infection to become dysplastic and progress to a fatal case of invasive cervical cancer is at least 30 years.[20] Additionally, the average age of females who die due to cervical cancer is at least 59 years while, the average age for adolescent girls and young adult female who die after HPV vaccination is 14 years and the median age is 15 years, exhibiting a *Years of Potential Life Lost* (YPLL) that exceeds 75 for each girl. Our research or cervical cancer associated death was also consistent with cancer data available from the National Institute of Health (NIH) Surveillance and Epidemiology End Results (SEER).

DISCUSSION

Similar to other pharmaceutical products, vaccines may exhibit adverse reactions. However, compared to complications and suffering associated with the actual vaccine-preventable disease (VPD) itself, these events should be mild, self-limiting, and predictable. As with all medical interventions and vaccines there is always a potential for a very small proportion of individuals to develop severe adverse events or even die. Extensive studies and clinical trials involving approximately 21,000 girls and women in the United States and worldwide were conducted before FDA approval to evaluate the vaccine safety and efficacy. Unexpectedly, there have been large numbers of reports on

rather serious adverse reactions and events among adolescent girls and young adult females who received one or more doses of the vaccine. More than any other currently used vaccines, *Gardasil* was linked to higher incidence rates of reported adverse events including fainting, serious neurological impairments, coagulation disorders and death.

No vaccine is 100% safe and effective, and *Gardasil* is designed to provide partial immunization against an infection that is extremely prevalent, often has no symptoms, and usually resolves spontaneously without negative consequences. Probably the quadrivalent HPV vaccine was cleared too soon by FDA in order to be used for the general public. A process that normally takes three years from the initial application to the final approval was reduced to about a year. However, both the FDA and CDC continue to assure the public that the vaccine is safe and effective, and its benefits continue to outweigh its risks. On the other hand FDA and CDC have taken active steps to alert healthcare providers to be more vigilant, watch for, and report any severe adverse events after vaccination with *Gardasil.* Additionally, the FDA cautioned providers to carefully observe those who receive *Gardasil* for at least 15 minutes after vaccination to avoid potential injuries due to falls in the event of prolonged syncope. Fainting is regarded as a common event after injections and vaccinations, especially among female adolescents. Yet, profound loss of conscious even for a short time, more frequently observed after *Gardasil*, resulted in many uncontrolled falls and caused serious injuries. Such injuries should be prevented by closely observing the vaccinated person. Post-vaccination observation is crucial to prevent syncope and injuries associated with fainting.[21] Furthermore, the FDA recently directed the vaccine manufacturer to revise the *Gardasil* label insert in order to reflect such precautions and warnings.

Similar to all other VAERS reports, serious adverse events reported after *Gardasil* may or may not have been caused by the vaccine itself. Based on that, there should be a no difference or just a little in the type, frequency, and severity of vaccine-related adverse events reported to VAERS following *Gardasil* or any other vaccines administered to teenagers, especially if they have a similar route of administration. The three vaccines *Menactra, Gardasil,* and the monovalent H1N1 novel influenza virus vaccine were all developed to prevent or control infectious diseases; all three targeted similar or comparable age groups; are administered intramuscularly to adolescent girls, teenagers, and young adult females; and the number of distributed doses for each vaccine was comparable. Nevertheless, the overall adverse events reporting rate following *Gardasil,* 56.53 per 100,000, was significantly higher than that after *Menactra* or after the H1N1 influenza vaccine which were 16.08 per 100,000 and 8.2 per 100,000, respectively.

It is important to emphasize that the rate of adverse events observed and reported during the *Gardasil* clinical trials conducted prior to FDA approval, was significantly lower than this currently observed rate. Such findings could be partially attributed to a *self-selection bias* of the trial subjects and providers. Similar to most of the randomized pharmaceutical clinical trials healthier subjects and more confident providers tend to participate more in such well funded studies. Additionally, trials' physicians and subjects tend to adhere to strict protocols and follow frequent reminders to comply with the manufacturer's recommendations.

VAERS reports generally indicated negative health outcomes or events that occurred during or after vaccination with *Gardasil*. Nevertheless, it provided excellent temporal relationships between vaccination and the development of these adverse events.

Most of the negative serious health outcomes including death and the majority of mild adverse events occurred less than two days after vaccination. Such a well-defined temporal distribution could probably link these events to the vaccine rather than to chance or other patient or provider-related risk factors. Although data and reports from VAERS are not fully verified or controlled for quality and completeness, CDC and FDA agree that VAERS reports are valid and reliable; especially, when properly used for comparing discrete safety measures among different vaccines. However, experts remain divided and many are uncertain whether rare, serious, or extreme adverse events constitute a convincing argument to stop recommending and administering *Gardasil;* pending further studies and evaluations. The patterns of adverse events reported in the U.S. after using *Gardasil* are similar to those observed after the implementation of population-based vaccination campaign with *Cervarix* in the United Kingdom and other countries in the European Union.

Consistent with the *Serotype/Genotype Replacement* phenomenon,[22] public health experts are concerned that eliminating the two most dominant oncogenic HPV genotypes 16 and 18 by *Gardasil* or *Cervarix* might allow for other HPV genotypes to become more aggressive; replacing these two genotypes in causing dysplasia and further reducing the effectiveness of the vaccine. Recent experiences with other vaccines such as *Prevnar* validate these concerns. *Prevnar* provides selective and partial immunity and helps to protect younger children against the seven most prevalent strains of pneumococcal bacteria that previously caused most of the serious pneumonia and respiratory infections. However, after a few years of using *Prevnar*, several national studies and vaccine monitoring systems observed that children started to develop pneumonia due to more

than 80 other pneumococcal bacteria strains that were not covered in *Prevnar*. Subsequently the manufacturers of *Prevnar* are adding to the vaccine six new strains/serotypes of the pneumococcal bacteria. However, there is no evidence that the new and improved *Prevnar 13* will have better performance than the original one.

CONCLUSIONS AND LESSONS LEARNED

- The FDA and CDC regularly verify VAERS data and according to most recent reports the rate of adverse events associated with the HPV vaccine is not above expectation. No common medical patterns were identified to link such events to *Gardasil* or to suggest that they were caused by the vaccine. According to these reports deaths and serious injuries reported after *Gardasil* could be coincidental, and explainable. However, the temporal distribution of such events is worthwhile being evaluated as most of those who died or developed severe adverse events were cluster in time around the vaccination event.
- Post-licensure safety surveillance can reveal previously undetected adverse events. Clinical reviews of targeted medical records and verification of case reports to VAERS following *Gardasil*, in addition to comparing morbidity and mortality after different vaccines are essential to assess vaccine safety.
- Frequency and severity of adverse events associated with a vaccine should not be perceived as vaccine-related only. Such events could also be patient-related especially if the recipient has other co-morbidities (*e.g.,* pre-existing chronic conditions or impaired immune response). Additionally, the individual health status and other circumstances around immunization could play an essential role; especially

if the vaccine was administered during an incubation/latency period for serious subclinical disease or during recovery after long and debilitating illnesses.

- Compared with other vaccines, the disproportional reporting of serious and non-serious adverse events after *Gardasil* may reflect significant differences that exceed expectations. However, the significance of such observation must be tempered with limitations of passive reporting systems such as VAERS and balanced with a well documented underreporting of adverse events following vaccination.
- Most HPV infections are short lived and are not associated with cancer. More than 86% of American females had been infected with HPV at some point in their lives. However, almost all of those were able to clear the virus without any intervention and will suffer no apparent short or long-term negative health consequences.
- Persistent infections with oncogenic HPV genotypes are required but insufficient risk factors for cervical cancer. Assuming that *Gardasil* will be extremely effective in preventing two of many other infections related to oncogenic HPV genotypes, it is not credible or clear how that will be translated in preventing cervical cancer.
- Similar to certain very important essential drugs and vaccines that are needed for urgent use to prevent diseases and control infections and pandemics, *Gardasil* was fast tracked through the FDA system for unclear reasons. Meanwhile, there were no newly emerging or reemerging public health threats or healthcare emergencies, or any looming pandemics of cervical cancer.
- Increased reporting of adverse events associated with the HPV vaccine, compared to what has been observed in association with other vaccines, requires additional studies

to evaluate determinants of such disproportional reporting especially for syncope, seizures, and blood clotting disorders.

- The Vaccine Safety Datalink (VSD) is currently using real-time surveillance studies to evaluate multiple adverse events especially those related to blood clots and pulmonary emboli. Projects to enhance the surveillance for Guillain-Barré syndrome are being developed and several national studies are currently using VAERS, VSD, and other data system to evaluate the burden of this disease.
- Differences between *Gardasil* and other more popular childhood vaccines such as MMR are substantial. MMR was developed to prevent serious acute and highly infectious diseases such as measles, mumps and rubella with relatively high case-fatality rates. The benefits of vaccines such as MMR are evident and already validated and established by numerous long-term epidemiological studies in America and worldwide.
- Recently the National Vaccine Information Center (NVIC) requested a temporary suspension of the FDA license for *Gardasil* pending additional studies after the increasing reports of death and permanent disability, and several law-suits against the manufacturers in the U.S. and Europe. Additionally, recent national surveys regarding *Gardasil* showed that healthcare providers are getting more cautious and conservative, and increasingly low proportions of females are willing to accept the risk. [23] At what level harmful adverse effects resulting from vaccines or any other medical intervention are considered excessive, and when can we conclude that risks associated with novel medical or surgical interventions may outweigh potential benefits?

- There is compelling evidence that the vaccine lacks therapeutic efficacy among women who have had prior exposure to one or more of the HPV vaccine genotypes. *Gardasil* is less effective when given to older females whose chances to have been already infected increase with age. Careful analysis of clinical trials data showed that *Gardasil* could promote the dysplastic process among those infected with the HPV vaccine genotypes.
- It is debatable if parents of young children or healthcare providers would continue to accept such a relatively high rate of serious adverse events when a better level of cancer prevention can be achieved with a regular cervical cancer screening including Pap smear testing. Even when a woman is already known to be infected with one or more persistent oncogenic HPV types, her chance of developing invasive cervical cancer is extremely low if she has a competent immune system and regularly undergoes Pap smear screening.
- Cervical cancer was one of the most common causes of cancer death for American women. However, between 1955 and 1992 the death rate due to invasive cervical cancer declined by 77%. Since then the rate has continuously declined by nearly 4.2% a year.[24] The main reason for this decline is the increasing use of regular Pap testing. Modern cervical cancer screening can detect very early dysplastic changes in the cervix. It can also identify early cervical cancer in its most curable stage. Almost all women who undergo regular Pap smear screening are not at risk for developing invasive cervical cancer or dying from it.[25]
- *Gardasil* is recommended for perfectly healthy young females who have extremely low probability for developing invasive cervical cancer later in life and even lower or

"negligible" chance of dying from it decades later. So if the risks associated with the HPV vaccination appear to be low, the immediate and long-term benefits of the vaccine appear to be negligible.

- It is important to remember that the HPV vaccine will not eliminate the need for cervical cancer screening. However, many public health experts are worried that it could result in a significant decrease in the rate of those undergoing regular Pap tests, which in turn could lead to an increase in the incidence of cervical displasia and cancer. Given that cervical screening continues to be very important and critically needed for those who are vaccinated and those who are not, then *Gardasil* seems to be an extra risk for a very little medical or practical health benefits.
- Under the current safety profile, it seems that the benefits of vaccination for an almost always harmless virus such as HPV do not outweigh the risks and even rare adverse events in a perfectly healthy young girl may be too much of a risk.
- New vaccines are not always without serious health repercussions. Such adverse effects sometimes only show up years after the FDA has approved the vaccine. Recently the FDA suspended the Rotavirus vaccine after several reports and studies demonstrated that it was unsafe for children.
- CDC is currently developing a new vaccine safety monitoring systems that will augment existing surveillance tools, estimate background rates for selected medical conditions, and focus on specific health events such as GBS, and ALS. It is expected that data from the new system would support epidemiological studies in assessing association and causality. Such systems will enhance the ability to determine whether

increasing rates of serious adverse events reported to VAERS after *Gardasil,* are attributed to a valid reporting bias or due to real safety differences among vaccines.

- To synthesize and objectively evaluate data on the HPV vaccine safety, a nongovernmental working group has been established. The group is formed from childhood immunization experts representing different federal and state advisory committees as well as experts in internal medicine, pediatrics, immunology, and vaccine safety. The group will meet regularly and will provide reports to the public, healthcare providers, and policy makers.

RECOMMENDATIONS

- *Gardasil* would be most effective if administered before starting sexual activity because virtually all those who are sexually active are either exposed to or are already infected with HPV.
- Regardless of its potential to prevent two oncogenic genotypes of HPV-related infections, *Gardasil* should never be administered without a prescreening for HPV, because it has the potential to worsen existing cases. It is highly recommended that girls be tested prior to their first inoculation to check for the presence of HPV in their system.
- Although the number of fatal and other serious adverse events is not extremely high, such unfavorable outcomes are real. They should be regularly monitored and thoroughly evaluated. No causative relationship between receiving *Gardasil* and the observed adverse events has been established. However, reports of noteworthy

temporal associations such as those demonstrated in our research should be analyzed very seriously.

- Prudence is strongly recommended in view of many unanswered questions regarding effectiveness, duration of protection, safety and potential adverse effects that may emerge in future.

In order to develop the national capacity for early detection and the rapid identification of adverse events and signals, it is our recommendations that VAERS be enhanced by:

- Providing VAERS contact information on the HPV vaccination record cards.
- Increasing the advertisement of VAERS in medical journals, provider updates and medical literature.
- Encouraging healthcare providers and the public to report adverse events to VAERS in a timely manner.
- Improving communication with state vaccine safety coordinators.
- Increasing the number of experts who could verify reports, obtain, and review medical records.

Additional recommendations include:

- Comprehensive and timely vaccine safety monitoring and response systems are necessary to early detect potential increases in adverse health events and for population-based studies and evaluations.

- VSD and other systems should continue to monitor adverse events following HPV vaccination in order to determine long-term adverse events and negative health outcomes. Because of its ability to follow cohorts of vaccinated and unvaccinated persons over time, the Vaccine Safety Datalink (VSD), which represents large electronic data systems, could be of value to detect associations between health events and the vaccine. VSD may have the capability to test, support and strengthen the findings generated by VAERS reports.
- Close monitoring of vaccine performance and ongoing data collection regarding its short and long-term impacts are strongly recommended in order to guide informed public health decisions.

STUDY LIMITATIONS

- The number of HPV vaccine doses that were already used is unknown and there are no national estimates available at the present time. As such, it is essential to emphasize that computed rates of adverse events may underestimate the magnitude of the problem especially if not all distributed doses were used. However, the consistent use of "standard" denominators such as the number of distributed doses is a common practice that is used for conducting comparative studies among the different vaccines.
- VAERS data can early detect valuable signals (*i.e.,* above expectations, new, unexpected or rare adverse events). An adverse event reported to VAERS after vaccination could have conceptually occurred due to the chance, but, also it might have been causally related to the vaccine. While extremely useful to determine

association, current data and information available from VAERS are inadequate to demonstrate that receiving a certain vaccine is causing specific negative health outcomes or could certainly lead to the development of such adverse events.

- Many of the reports on adverse events resulting after HPV vaccination were initially submitted by the vaccine manufacturer and did not include adequate information to support epidemiological investigations or contribute to the national ongoing studies and research on the vaccine safety.
- Due to the fact that adverse reactions to medication tend to be underreported, the actual number of negative health events and outcomes associated with *Gardasil* is probably higher. Nevertheless, currently there are no studies to evaluate reporting inadequacies or validate such observations.
- Underreporting to VAERS, and using surrogate denominators in calculating rates, in addition to several unknown differences in the background populations who received multiple vaccines, probably, made our complex comparison less specific.
- Data from VAERS indicated that the overall reporting rate after HPV vaccination was higher than the rate of reports after other vaccine. Such findings create serious concerns about the safety of HPV vaccine. However, currently there are no pre-determined cut-off values for reporting levels, or well defined measures and indicators to determine the safety of new vaccines.
- Although monitoring and analyzing three year's worth of VAERS reports and data do not provide adequate evidence to draw conclusions, our study findings might serve as an early alert regarding the safety of the HPV vaccines. However, some of our observations could have been generated due to an extraordinary effort to weekly track

and review VAERS data, an enhanced provider reporting and a heightened public awareness regarding the vaccine safety.

- Public health experts are concerned about possible side effects that could become apparent only after the vaccine has been more widely used over longer periods of time. Since long-term data is not yet available, it is unknown if or when additional more serious long-term adverse events will emerge in the future.
- Pre-licensure clinical trials were limited in size and were not designed to detect rare or long-term adverse events associated with the HPV vaccine. Moreover, due to a selection bias such studies tend to enroll healthier volunteers and well trained physicians who are probably more prone to participate.
- Findings from this research are subject to additional limitations including:
    a. Under-reporting from the public as most of the VAERS forms are complex, lengthy and not easy to complete. Especially that such reporting is not mandatory; it is done on a voluntary basis and requires some technical skills.
    b. As a voluntary reporting system, VAERS reports provide only preliminary information. Final diagnoses could be validated later through medical records' review. However, even when such diagnoses are validated, VAERS reports may not be adequate to support some conclusions. Time-frames between vaccination and the occurrence of adverse events or submitting reports to VAERS could be challenging to ascertain.
    c. Long-term medical conditions that might develop weeks, months, or years after vaccination could not be captured in this VAERS analysis, which included only three years of post-marketing experience.

Table 3. *Gardasil* Reported Adverse Events November 2006 - November 2009

Injection Site		
Pain	4912	31.03
Swelling	3433	21.69
Erythema	2950	18.64
Pruritis	240	1.52
Bruising	238	1.50
Systemic		
Pyrexia	5715	36.10
Syncope	2068	13.06
Nausea	2951	18.64
Seizure-like activities	873	5.51
Headache	4790	30.26
Unintentional injury	157	0.99
Dizziness	3212	20.29
Diarrhea	1622	10.25
Vomiting	1435	9.07
Cough	867	5.48
Coagulation disorder	112	0.71
Vascular accident	516	3.26
Respiratory distress	134	0.85
Upper respiratory tract infection	406	2.56
Malaise	399	2.52
Arthralgia	247	1.56
Insomnia	239	1.51
Heart Failure	88	0.56
Autoimmune		
Arthralgia/Arthritis/Arthropathy	760	4.80
Autoimmune Thyroiditis	7	0.04
Amyotrophic Lateral Sclerosis	11	0.07
Diabetes Mellitus	144	0.91
Erythema Nodosum	5	0.03
Hyperthyroidism	36	0.23
Hypothyroidism	49	0.31
Guillain-Barré Syndrome	52	0.33
Inflammatory Bowel Disease‡	13	0.08
Multiple Sclerosis	21	0.13
Nephritis	20	0.13
Optic Neuritis	16	0.10
Pigmentation Disorder	42	0.27
Psoriasis	33	0.21
Raynaud's Phenomenon	18	0.11
Rheumatoid Arthritis	67	0.42
Scleroderma	11	0.07
Stevens-Johnson Syndrome	5	0.03
Systemic Lupus Erythematosus	12	0.08
Anaphylaxis	109	0.69

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Chapter 5

STUDY CONCLUSIONS

STUDY CONCLUSIONS

Most of HPV infections are transient, short lived and are not associated with cancer. Infections with oncogenic HPV genotypes are necessary but insufficient carcinogens for cervical cancer. A susceptible host with a weak immune system, lack of access to preventive health care services and decades of not undergoing cervical cancer screening are just a few of the risk factors for developing invasive cervical cancer.

Vaccination with *Gardasil* provides partial immunity against an extremely prevalent biological agent, often has no symptoms, and usually resolves spontaneously without negative consequences. However, even if the vaccine turns out to be very effective in preventing infections related to HPV genotypes 16 and 18 that will not necessarily translate into preventing cervical cancer. Additionally, eliminating these two most dominant HPV genotypes may create a favorable environment for other genotypes to fill the niche and dominate.

Determining that the benefits of a medical intervention outweigh its risks is closely related to the disease entity targeted for prevention, treatment, or control. For instance severe adverse events associated with the human immunodeficiency infection (HIV) medication are universally accepted because such medications are effective in preventing the acquired immunodeficiency syndrome (AIDS) and reducing morbidity, mortality, disability and hospitalization from HIV. Actually, there is no cervical cancer outbreak or an epidemic. In the contrary, for more than half a century observed trends of cervical cancer morbidity and mortality are showing significant decline that is due to a very effective population based screening programs.

The HPV vaccine was not proven effective in preventing cervical cancer, and even minimal adverse events may not be tolerated especially among young and healthy girls whose risk to develop or die due to cervical cancer is zero. Additionally, such risk continues to decrease every year due to regular Pap testing.

Vaccination with *Gardasil* may provide a false sense of security as it does not provide any cross protection against infections caused by more than 120 HPV genotypes not considered in the vaccine. Additionally, it doesn't provide protection against other sexually transmitted infections and diseases such as Chlamydia, Gonorrhea, and syphilis. Those properly vaccinated with *Gardasil* must continue to follow safe sex practices.

It is important to emphasize that regular cervical cancer screening continues to be required for all those who receive the vaccine. Public health experts are concerned that vaccinated females may believe that they are protected against cervical cancer and may stop undergoing regular cervical cancer screening. While screening is usually required once a year or even less frequently among those who have had three consecutive negative Pap tests, vaccination with *Gardasil* requires three office visits in less than a year. Additionally, the need for booster shots may further increase the risk for adverse events and the costs associated with the office visits and the vaccine itself.

It is important to emphasize that cervical cancer screening is a well established comprehensive public health approach that provides numerous opportunities to prevent, early detect, and treat cervical infections, displasia and cancer. Additionally, many cases or diabetes mellitus, heart diseases, hypertension, morbid obesity and many other communicable or chronic can be early detected during the physical exams provided for women who undergo regular annual screening. Cervical cancer morbidity and mortality

rates are sensitive indicators and accurate measures for community health and the public health system as a whole.

Clinical trials and studies conducted before the FDA licensure are the best available tools to assess safety and effectiveness of new medical interventions. However, they are by no means error proof. Even if a new medication or a vaccine were found to be safe during clinical trials and were approved by FDA for population-based use, post-marketing or post-licensure safety surveillance continues to be essential. The recall of the arthritis medications Vioxx and Celebrex few years ago, and the recent recall of the Rotavirus vaccine and the diabetes medication Avandia are just few examples that post marketing surveillance can be instrumental in detecting serious adverse events that were missed during clinical trial.

Based on our research *Gardasil* was found to be less effective than regular cervical cancer screening. It was linked to relatively high rates of serious adverse events and it was found to be severely underutilized in Nevada and probably nationwide. The main reason for the decline in cervical cancer incidence and death is the increasing use of regular Pap testing. Pap testing is safe and it works for everybody. Additionally it is accessible for almost everyone, it provides opportunities for females to have regular medical evaluations where many other diseases and conditions can be early detected and case managed. Death due to cervical cancer continues to occur because a significantly large number of females have no access to regular Pap smears, and/or other diagnostic tests. Females who get regular Pap tests almost never die of cervical cancer. Invasive cervical cancer is completely preventable and the death rate from it should be “zero” percent.

It seems that the benefits of vaccination for an almost always harmless virus such as HPV do not outweigh the risks. Given that cervical screening continues to be very important and critically needed for those who are vaccinated and those who are not, then *Gardasil* seems to be an extra risk for a very little or no medical or practical health benefits.

Evaluating this vaccine in the first three years of utilization is just the start. Long term population based studies are required and it is our hope that this real-time research would set the stage for more extensive population-based studies such as:

- Evaluating the effectiveness of the vaccine in preventing cervical cancer itself. Due to ethical consideration, cervical cancer was not considered as an endpoint in the clinical trials. Withholding treatment for subjects who developed severe cervical displasia was considered unethical and subsequently all trial subjects who developed severe dysplasia received conventional treatment.
- Evaluating and monitoring the impact of eliminating HPV genotypes 16 and 18 on other HPV genotypes.
- Evaluating the temporal distribution of death and other serious adverse events associated with *Gardasil* could be of a great value to determine associations or causal effects of the vaccine.
- Evaluating the effectiveness of the vaccine in areas of the world where there are no population-based cervical cancer screening programs. Certainly that could be a challenging task especially that the vaccine is by far more expensive than screening.

- Evaluating the true prevalence of HPV infections associated with genotypes 16/18 among the general population.
- Determining the maximum allowable rate of reported adverse events associated with newly licensed vaccines.
- Evaluating the impact of improving access to preventive healthcare services on decreasing cervical cancer morbidity and mortality.
- Evaluating the added value of regular cancer screening on the overall public health status of a community (*e.g.*, healthier women, families, and children).
- Assessing the value/cost-effectiveness of regular HPV testing prior to administration of the HPV vaccine.
- Evaluating causality between the HPV vaccine and observed serious adverse events.
- Monitoring and evaluating the disproportionate reporting rate among different vaccines based on actual levels of utilization.
- Evaluating duration of immunity against HPV genotypes 16/18 acquired through vaccination.
- Surveying healthcare providers' knowledge, practices and attitudes regarding the value of *Gardasil.*
- Conducting case-control studies of those who developed/did not develop severe and fatal adverse events associated with the HPV vaccine.
- Conducting prospective cohort studies to determine the vaccine's effectiveness, risks, benefits, and duration of protection.
- Estimating the rate of compliance and completion among those who started the vaccine.

- Evaluating rates of completion of other vaccines such MMR and DTap among VFC providers in Nevada.
- Estimating the years of potential life lost (YPLL) due to mortality associated with *Gardasil* to quantify and measure the burden of *Gardasil* especially that the average age of deaths associated with *Gardasil* was 14 years, while most of the deaths due to cervical cancer occurred at older ages.