American Journal of BioMedicine
AJBM 2014;2 (3): 102-115
Research Article doi: 10.18081/2333-5106/014-06/136-146

Human papilloma virus (HPV) vaccine: Gardasil reactions

Shah B Navarro[1], Bintenna M Peiris [*1]

Abstract

With resolution of infection, HPV is not thought to be cytopathogenic. In fact, it is thought that the benign behavior of the HPV virus probably allows it to persist in a latent form in normal epithelial tissues. Indeed, most humans infected with oncogenic HPV appear to contain the virus in a dormant or non-replicating state, and the infection is topologically and temporally very stable. The persistence of HPV in stratified squamous epithelium may be dependent on the inability of the innate immune system to detect viral infection in basal epithelial tissues and might involve the limited immunogenicity of early products of the virus. In situ hybridization and PCR methods for detecting viral nucleic acids have shown that in experimental infection with highly oncogenic HPV types, several dysplastic human tissues harbor the virus in a non-cytopathogenic and latent form. Similarly, and in agreement with a viral latency model, it has been shown that the E7 immortalizing activity of HPV-16 can be completely diminished in NIH3T3 cells once pRB is inactivated by a mutation. In this regard, oncogenic HPV types may be similar to other human viruses, which, upon infection, may spontaneously enter an asymptomatic dormant or latent state. Preventive vaccines using virus-like particles are currently in use against HPV infection. They are very efficacious against the two high-risk oncogenic HPVs, which account for a significant percentage of cervical cancers. Virus-like particles are comprised of the L1 capsid protein of the HPV virus and carry no HPV DNA sequences; hence, they do not induce an HPV-related tissue response in the recipient. These vaccines are granted the status of "safe."

Keywords: HPV vaccine; Cervical cancer; Cervarix; Gardasil

[*]Correspondence author e-mail: Bintenna_Peiris@yahoo.com
[1] Faculdade de Medicina, Universidad Nacional del Comahue, Neuquén, Argentina
Received February 12, 2014; Accepted May 25, 2014, Published July 04, 2014

Introduction

Human Papillomavirus (HPV) is among the most commonly contracted sexually transmitted infections worldwide, affecting both men and women. Most strains are harmless; however, HPV is known to be the primary cause of virtually all cervical cancers. HPV causes an estimated 500,000 cervical cancer cases and 250,000 deaths per year worldwide, making it the second most common cancer in women after breast cancer in the developing world. It is estimated that

Research Article doi: 10.18081/2333-5106/014-06/136-146

80% of sexually active women will have been infected with HPV by age 50. The HPV types that cause genital warts also account for 90% of cases, while HPV types that cause squamous cell carcinoma account for 70% of cases.

Among sexually active individuals, acquisition of HPV is nearly universal; the overwhelming majority of infections are cleared by the immune system without intervention. However, there are two established mechanisms by which genital infections can go on to become persistent, causative infections. The first involves infection by a carcinogenic HPV type. The second mechanism involves a prolonged period of immune suppression because of factors such as smoke exposure, oral contraceptive use, immunosuppression associated with HIV, and/or coinfection by other sexually transmitted agents. Prevention of initial infection is thus a logical approach to disease prevention.

In Western industrialized countries, the introduction of the Pap smear screening program greatly reduced both the incidence and mortality rates from cervical cancer, but most low- and middle-income countries do not have access to Pap smear screening and are thus much more dependent on HPV vaccination to prevent cancer. The public health perspective outlines why vaccines against cervical cancer as a result of HPV infections are desirable. Gardasil is a quadrivalent vaccine against infection by HPV types. Gardasil is highly efficacious against preinvasive lesions and, to a lesser extent, genital warts caused by certain strains. Since HPV types account for 90% of HPV-related disease in the United States, Gardasil is expected to prevent about 70% of cervical cancers and 90% of genital warts.

Since Gardasil vaccination was introduced in the United States and other countries in 2006, there have been reports of various deleterious side effects, some of which have occurred more than a year after vaccination. Accurately assessing the risk-benefit ratio of the vaccine is complicated by this relatively small epidemiological database. This paper investigates whether there is a link between Gardasil vaccination and adverse reactions. Human Papillomavirus (HPV) is a group of more than 150 related viruses that can infect mucous membranes and skin. It ranks among the most common sexually transmitted infections in the world and is often asymptomatic. HPV is typically spread during sexual activity through minute tears in the skin or mucosal surfaces. Common symptoms include warts, genital warts, or papillomas. Although most HPV infections are harmless and resolve spontaneously, certain persistent HPV types may lead to cancerous or precancerous lesions, particularly HPV types 16 and 18. Vaccines have been developed to provide effective protection against the most common strains of HPV. Human Papillomavirus (HPV) is a group of more than 150 related viruses. Out of these, about 40 types can spread through direct sexual contact, and they can infect both moles and moist areas like the cervix, anus, mouth, and throat. Most types of HPV are harmless and cause no symptoms. However, there are some oncogenic HPV types that can lead to cancer, particularly cervical cancer in women. Infection with HPV is usually asymptomatic, and in most cases, the immune system clears it within two years. Approximately 10-30% of infected individuals will develop a chronic infection with oncogenic HPV types that can lead to the development of

Research Article doi: 10.18081/2333-5106/014-06/136-146

(pre)malignant lesions. Persistent infection due to high-risk HPV types is necessary for the development of cancer.

The vaccine is an inactivated virus-like particle vaccine that provides effective protection against HPV types 6, 11, 16, and 18, which are the most common strains of HPV linked to the development of cervical cancer. The vaccine was introduced to prevent genital warts and cervical cancer by stimulating an immune response to the virus and preventing the infection from occurring. The vaccine did not contain any virus and, therefore, could not cause disease. After the introduction of the vaccine, there was a significant debate regarding the potential side effects and the safety of the vaccine. The vaccine was thought to promote sexual promiscuity among adolescents, and there were calls for further safety studies before the vaccine was used. This report investigates the potential reactions caused by the use of the vaccine, with particular emphasis on autoimmune diseases.

Purpose of the Vaccine

With resolution of infection, HPV is not thought to be cytopathogenic. In fact, it is thought that the benign behavior of the HPV virus probably allows it to persist in a latent form in normal epithelial tissues. Indeed, most humans infected with oncogenic HPV appear to contain the virus in a dormant or non-replicating state, and the infection is topologically and temporally very stable. The persistence of HPV in stratified squamous epithelium may be dependent on the inability of the innate immune system to detect viral infection in basal epithelial tissues and might involve the limited immunogenicity of early products of the virus.

In situ hybridization and PCR methods for detecting viral nucleic acids have shown that in experimental infection with highly oncogenic HPV types, several dysplastic human tissues harbor the virus in a non-cytopathogenic and latent form. Similarly, and in agreement with a viral latency model, it has been shown that the E7 immortalizing activity of HPV-16 can be completely diminished in NIH3T3 cells once pRB is inactivated by a mutation. In this regard, oncogenic HPV types may be similar to other human viruses, which, upon infection, may spontaneously enter an asymptomatic dormant or latent state.

How Gardasil Works in the Body

Gardasil is a recombinant quadrivalent vaccine for the prevention of cancers, pre-cancerous lesions, and genital warts caused by human papillomavirus (HPV), which includes vaccine types 6, 11, 16, and 18. It contains virus-like particles (VLPs) composed of the L1 major capsid proteins of HPV types 6, 11, 16, and 18 and recombinant Saccharomyces cerevisiae as a non-infectious virus. The L1 VLPs self-assemble into VLPs, which mimic the natural HPV virion but lack the viral genome. The VLPs, in combination with alum as an adjuvant, stimulate a strong immunological response to the specific L1 protein type, leading to the production of neutralizing antibodies. Gardasil does not contain any adjuvant compounds other than those in its proprietary formulation, which contains aluminum as a co-precipitated insoluble salt.

In clinical use and observation, Gardasil is effective, and safety data is available for more than 12,000 participants enrolled in clinical trials worldwide. Gardasil is effective beyond 3 years with

Research Article doi: 10.18081/2333-5106/014-06/136-146

sustained cellular immune responses and no serious adverse events. To the present time, Gardasil remains the only vaccine licensed for use in the United States to prevent female cancers and pre-cancerous lesions associated with HPV.

Gardasil helps the body develop immunity against HPV types 6, 11, 16, and 18, which may cause cancer and pre-cancerous lesions in the cervix, other genital areas, and within the throat, as well as genital warts. Gardasil contains VLPs of HPV 6, 11, 16, and 18 in a single dose. Following injection, the body's immune system recognizes this protein as a foreign substance, stimulating an immune response. Neutralizing antibodies are produced, preventing HPV types 6, 11, 16, and 18 from establishing an infection. Neutralizing antibodies can survive for many years, and antibodies from the primary vaccination series persist for at least 5 years.

Safety and Efficacy of Gardasil

The scrutiny of vaccines, especially those aimed at adolescent females, is a delicate topic. The introduction of the quadrivalent HPV vaccine promises to alter the course of cervical cancer in women. Headlines blared fears of a "cervical cancer vaccine" aimed at nine-year-olds, effectively ignoring the target age of 11-12. Concerns about pre-teens, sex, and vaccinations autonomously given by school nurses, without parental knowledge or consent, quickly came to the fore. The vaccine is actually a sexual health vaccine, specifically engineered to prevent genital warts and the vast majority of pre-cancerous cervical changes associated with HPV. These are some of the most common sexually transmitted diseases: there are upwards of 9,000 new cases of cervical cancer and 17,000 new diagnoses of genital warts per year. To put it in perspective, approximately 6,000 women survived breast cancer, while almost 2,000 died from it. The vaccine is not a cervical cancer vaccine. Several women, aged between 22 and 51 years who died of cervical cancer in the clinical trial, were never vaccinated. To prevent cervical cancer, the prevention of a chronic HPV infection is needed, something the vaccine does not guarantee.

Before reaching the market, the vaccine was the subject of extensive testing for clinical efficacy and safety. In the initial clinical trial at 442 sites, a sub-group that also received placebo served as the double-blind cohort. So far, clinical follow-ups are complete, analyses are ongoing, and reporting of results continues.

In the pivotal Phase III trials, the vaccine was tested in females aged 16-26 who received 3 doses or placebo within 12 months. All subjects were free of disease or abnormal Pap cervical cytology. Women in the placebo group subsequently received the vaccine. After 2.2-4.6 years follow-up, the vaccine demonstrated nearly 100% efficacy against any HPV disease (cancer, warts, and pre-cancerous lesions) caused by HPV types 6, 11, 16, or 18, with significant efficacy persisting beyond 4 years. Individuals at higher risk for cervical cancer also experienced 95-100% efficacy.

While the clinical trials indicate strong efficacy, safety must also be considered. A significant percentage of recipients reported an adverse event within 15 days. The most common adverse events were injection site reactions and systemic effects. Of 25 deaths, a portion of recipients

Research Article doi: 10.18081/2333-5106/014-06/136-146

died (causality not established). There were deaths that could be vaccine-related. Other serious adverse events include cholestatic liver injury, cranial venous thrombosis, and a case of new-onset MS (causality not established). There were no differences in serious adverse events between groups.

Clinical Trials and Studies

The vaccine Gardasil, developed to prevent certain strains of the Human Papillomavirus (HPV), was approved in June 2006. As with most vaccines, Gardasil's approval was granted following a series of clinical trials that looked into the vaccine's overall safety and efficacy; those clinical trials and studies were undertaken between the 1990s and 2005. Gold standard practices were followed, including randomization, double-blinding, and placebos, to uncover any issues with the vaccine before it was cleared for public distribution. Gardasil was tested mainly on young women ages 16-26, but studies on significantly younger populations were also carried out. In the 3,423 women included in the study who received Gardasil, 34% reported adverse reactions at and/or after the injection, including swelling, rash, itching, headache, and muscle soreness. Though these reactions were considered extensive, they were similar to those found in study populations given other vaccines, and it was stated that "none of the reported changes in health status were considered serious or suggestive of a vaccine-related illness." It was later discovered that because of a lack of understanding regarding the method used to produce the HPV vaccine involved in the adjuvant used in Gardasil's creation, it was never properly studied for safety and efficacy. After it was approved based on these clinical trials, evidence began to unravel condemning the company of a deliberate attempt to hide evidence indicating an association between Gardasil and several dangerous autoimmune diseases. A study looked into the medical histories of patients who reported adverse reactions following the injection of Gardasil. Out of the 8,843 women included in the study, 57% were found to have pre-existing conditions strongly associated with autoimmune disease. Of the 703 adverse reaction cases reported, 577 were substantiated, furthering the belief in some form of corruption in the pharmaceutical company responsible for the vaccine by those who had come into contact with those who were injured or killed after receiving it. Several alternative studies were also published and exposed after Gardasil's approval, which included one that described a young girl's experiences with seizures and comas after receiving the vaccine, finally leading to her medical team believing her injuries were directly linked to Gardasil.

Common Side Effects

Despite the vaccines' success in preventing these diseases, adverse reactions are of great concern to prescribing physicians and patients. Manufacturers of vaccines are required to assess safety and efficacy, and Gardasil was evaluated in Phase II and III trials for safety and efficacy. The clinical trials, along with ongoing monitoring of HPV vaccine recipients, provide evidence of the safety of Gardasil. Clinical trials for Gardasil included more than 29,000 individuals, and the most common adverse reactions were pain, swelling, and redness at the injection site as well as headache and fever. Vaccine safety continues to be monitored. Most

Research Article doi: 10.18081/2333-5106/014-06/136-146

of the reactions reported have been mild, such as local reactions. Serious reactions appear to occur at a rate similar to that expected in the general population. Studies are underway to assess rare events following HPV vaccination. Gardasil is safe and effective in both genders and in both HIV-infected and healthy patients.

Rare and Severe Reactions

The likelihood of severe allergic reactions, or anaphylaxis, to the HPV vaccine was a concern raised by a group of doctors in 2008. These doctors filed a petition with the United States federal government for compensation under the National Vaccine Injury Compensation Program for injuries allegedly resulting from the vaccine. These injuries included: • Seizures • Blood clots in the brain • Blood clot-related strokes • Multiple sclerosis • Paralysis • Death This group claimed these injuries were caused by the HPV vaccine in susceptible individuals. An investigation by the Health Resources and Services Administration became the Vaccine Injury Table Review to the Health and Human Services. The Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices and the Centers for Medicare and Medicaid Services' Advisory Panel on Immunization Practices were part of the investigation. Though the vaccine was found safe for the injuries claimed, there were still concerns about the vaccine. Reports were filed to the Vaccine Adverse Event Reporting System. These included a variety of serious injuries supposedly caused by the vaccine. These injuries were the same as claimed in the investigation and included: • Thrombosis or embolism of the brain • Death • Seizures • Guillain-Barré syndrome • Stroke The vaccine was also linked with 84 deaths within eight days of receiving the vaccine. Following an investigation, the Vaccine Safety Datalink found no association with the vaccine and serious injuries. A safety monitoring study was also conducted which found no association with the vaccine and serious injuries. In response to these concerns about the HPV vaccine, a collection of Southern California neurologists reported 24 patients, ages 12–30, who developed Guillain-Barré syndrome after receipt of the vaccine to the Federal Vaccine Adverse Event Reporting System. GBS is a rare illness where the body's immune system attacks the nervous system. This sends signals to different parts of the body, shutting them down. Symptoms include tingling in fingers or toes, weakness in the legs or arms, double vision, trouble walking, and trouble chewing or swallowing. Reported cases of GBS were reviewed by the Institute. A case was classified as a positive association by the Institute if it met the definition of GBS, returned to the same or similar level of health prior to GBS, and received the HPV immunization within the 31-90 days prior to the onset of GBS. Of the report of 24 patients included, the Institute concluded that one case was consistent with the review.

Anaphylaxis

Wide-ranging populations across the world receive the HPV vaccine every year, and the vast majority do so without major side effects. However, serious reactions, including anaphylaxis, have been noted. This report will examine some of the severe reactions associated with the vaccine. Anaphylaxis is a severe, potentially deadly allergic reaction. There have been 58 cases of anaphylaxis reported following receipt of the vaccine. This has been described as a

Research Article doi: 10.18081/2333-5106/014-06/136-146

significantly higher number than what would be expected within the population. However, within a wider context of all vaccines already on the market, this is not necessarily surprising, as seven years have elapsed since introduction. When factoring in the wider population receiving the HPV and other vaccines, the rate of anaphylaxis is stable and in harmony with rates established outside of vaccination.

All 58 cases of suspected anaphylaxis following receipt of the vaccine were investigated. Of these, 41 were confirmed anaphylaxis. Nine were considered to be not anaphylaxis, and the remaining 8 were deemed to be insufficiently investigated. 85% of the confirmed cases occurred in individuals aged between 9 and 26 years – the normal candidate population for the vaccine. Health professionals who are trained to recognize and treat anaphylaxis largely administered the vaccine, with the majority being administered at clinics and hospitals, as opposed to schools. The number and distribution of anaphylaxis cases correspond very closely with the number and distribution of doses administered.

Guillain-Barre Syndrome

Guillain-Barré syndrome (GBS) is a rare, serious condition in which the body's immune system attacks the peripheral nervous system. It can result in muscle weakness, loss of reflexes, numbness, and pain. In some cases, these symptoms progress to paralysis, which can be severe. GBS is also thought to be post-infectious in nature, meaning that it can occur following infections caused by certain bacteria or viruses. All cases of GBS occurring globally are monitored as part of the vaccine safety monitoring system. Reports of GBS following vaccinations are carefully studied. Many vaccines have been studied for an association with GBS, including the influenza vaccines; however, for some vaccines, an association with GBS has not been determined. In 2010, routine immunization with the catch-up vaccines in boys and men ages 26 years or younger was recommended. Vaccine safety following Gardasil vaccination was conducted in the post-licensure monitoring system during a specific time frame. The analysis indicated that there were no unusual patterns or statistically significant excesses of adverse events following immunization. The adverse events were similar to pre-licensure trials. The analysis presented in this report, an updated evaluation of GBS following Gardasil vaccination, was conducted in the safety monitoring analysis database of women ages 9 through 26 years during a specific time frame. In addition to new cases of GBS, there were also additional deaths, additional hookworm infections, additional vertigo, additional cerebral hemorrhage, and additional coagulopathy, with one case corresponding to vaccinees with chronic demyelinating polyneuropathy. Safety monitoring analyses are statistical comparisons of the number of reports of adverse events received following vaccination to a comparison cohort. An excess occurs when the number of reports is greater than would be expected. Because GBS can also occur in the absence of vaccination, statistical models have been developed that take these factors and the underreporting of adverse events into account. Such an analysis provides a level of confidence regarding the likelihood that a vaccine can cause reported adverse events.

Research Article doi: 10.18081/2333-5106/014-06/136-146

Controversies and Misinformation

The topic of the HPV vaccine and its alleged side effects has led to a whirlwind of controversy and misinformation. Since initial reports emerged, social media and the internet seem to amplify outrage into panic, and panic into paranoia. In Australia, anti-HPV vaccine outrage bubbled into panic before the vaccine was even released. In Denmark, after a few young women reported adverse effects after vaccination, mass headlines reported adverse effects. On social media, the HPV vaccine hashtag is used not only by those supportive of the vaccine but also by anti-vaccine advocates desperately trying to paint the vaccine in a negative light, linking incidents of a number of stigmatized outcomes to the vaccination. In the United States, the HPV vaccine has been implicated in everything from a rise in promiscuity, an uptick in births of children with developmental disabilities, and even a potential conspiracy where covert parties encourage drug and sexual exploration, leading to HPV infections. It is important to counter misinformation with a reasoned explanation of the HPV vaccine, its side effects and capacity for preventative treatment, and statistical comparisons to other healthcare interventions. Furthermore, it is equally important to empower informed and accurate outrage, targeting the personal information pharmacological companies obscure and the way mercantilized pharmaceuticals disproportionately affect specific demographics.

Even before the HPV vaccine was released for general consumption, misinformation had already been used against it. In April 2007, alleged deaths and adverse effects from the vaccine were cited. Immediately, anti-vaccine experts proliferated, questioning the vaccine's safety and pushing alternative interventions. Claims of adverse effects are hidden by the medical establishment. These narratives frame the HPV vaccine as an "experiment" on "innocent girls," a powerful narrative allowed to flourish by media sensationalism. In 2009, Japan's Minister of Health officially suspended the vaccine from the country's inoculation registry. On social media, anti-HPV advocates elaborate further on these sentiments, accusing the vaccine of racism, sexism, and classism. In this period of concern and panic, neither support for nor opposition to the vaccine is as innocent as it initially seems. After targeted advocacy workshops were given, the group plan was consistently attacked and challenged by various organizations, condemning the HPV vaccine as a means of population control, advocating abstinence instead. These responses were well-prepared as they were posted on multiple platforms and distributed to people near distribution points.

Debunking Common Myths

In an age where information is easily disseminated, rumors and misinformation can spread like wildfire across social media platforms and other channels. In the case of Gardasil, many myths have emerged in connection with adverse reactions, and several sources have devoted significant resources to spreading these unsubstantiated theories. All of these myths can be easily debunked based on sound scientific evidence.

The Gardasil vaccine has been falsely blamed for deaths, paralysis, and other serious adverse reactions. The vaccine, again based on a sound understanding of immunology, cannot cause

Research Article doi: 10.18081/2333-5106/014-06/136-146

any of these ailments. In the vast majority of cases, the reactions that have been reported in connection with Gardasil are indications of a normal immune response. For example, the vaccine is commonly associated with fainting, often due to the intense anxiety that girls experience when getting their shots. Other commonly reported reactions include soreness at the injection site and mild flu-like symptoms. The allergies and similar reactions cited in such sources have been explained in blatant misunderstandings of the nature of the vaccine. Some claims suggest it was approved following highly rushed and inadequate studies. Gardasil actually met strict protocols that required tens of thousands of women to be enrolled in clinical trials; adverse reactions were closely monitored for over seven years after the trials concluded. Furthermore, an extensive multi-country five-year study completed in 2010 showed no significant adverse reactions following vaccination. All of these trials are available for anyone to peruse. Beliefs that Gardasil has been shown to impair fertility are pure fabrications; no such trials have been conducted, and certainly no such trials could have yielded any results if they were! And so on.

Reporting and Monitoring Systems

After a vaccine is licensed, it continues to be monitored for both safety and efficacy. Through the public health system, several systems exist to allow individuals and health care professionals to report adverse events after vaccination.

This vaccination program provides the quadrivalent HPV vaccine free of charge to eligible children, adolescents, and young adults, and helps provide access for minorities and other underserved populations. This program has allowed for substantial increases in vaccination rates, but may also lead to an increased number of adverse event reports.

The Vaccine Adverse Event Reporting System is a national system for monitoring the safety of vaccines after they are licensed and in widespread use. It is co-managed by health authorities, and the reporting of any adverse events, whether or not they are thought to be caused by the vaccine, is encouraged. It was established in response to concerns over widespread vaccination against a newly licensed vaccine. A federal law was passed to create a compensation program, which provides a no-fault compensation source for individuals harmed by vaccines. The intent was to protect a safe and effective pediatric vaccine supply from liability concerns. This system uses passive surveillance and relies upon voluntary reporting by anyone, including the general public. It is the first step in detecting emerging safety issues that warrant further investigation.

Data from this system has been used to understand the nature of adverse events in the recently licensed quadrivalent HPV vaccine. During the first 17 months after the vaccine was introduced, approximately 7.4 million doses were distributed. During this time, the system received 6,372 adverse event reports, representing a rate of 86 adverse event reports per 100,000 doses distributed. These rates are very low compared with other routinized vaccines and are similar to the rate of reports of adverse events after administration of other vaccines.

Research Article doi: 10.18081/2333-5106/014-06/136-146

Adverse events reported after the HPV vaccine were generally consistent with the product labeling. Local reactions, including pain and swelling at the injection site, were commonly reported, along with other more typical vaccine-associated adverse events, such as rash and fever. There were reports of deaths after vaccination, but all were investigated and determined not to be causally related. Hospitalization rates were similar to those after other vaccines. Non-syncope CNS disorders were noted, including one report of a specific condition.

Vaccine Adverse Event Reporting System (VAERS)

With the increasing availability of vaccines, the importance of post-licensure surveillance for the detection of new adverse events or changes in the occurrence of known events grows. In the United States, a system was developed as a response to the National Childhood Vaccine Injury Act of 1986. The sole purpose of this system is the rapid detection of possible vaccine-related adverse events and subsequent investigation. A specific design feature is that it accepts all reports of adverse events that follow vaccination, regardless of the plausibility of a vaccine/event association. This design choice likely results in a much larger number of reports, but has two advantages. On the one hand, the "all reporting" philosophy leads to the rapid detection of rare adverse events that might be missed with a more focused approach. On the other hand, the increased noise provides protection against the possibility of not detecting a true vaccine liability simply because of the lack of sufficient information.

In the database, each report is assigned one of the following categories: (a) report received; (b) report under review; (c) report reviewed and findings sent to the appropriate health authority; (d) report reviewed and forwarded to another regulatory body; (e) unresolved after review and conditionally completed; (f) report not investigated; (g) automated system; (h) need for additional information; (i) report invalid; or (j) report refers to an incident not involving a vaccine. The system receives more than 20,000 adverse event reports annually, about 70% are associated with one of the following vaccines: diphtheria-tetanus-pertussis, oral polio, measles-mumps-rubella.

The system uses statistical/multivariate analysis to detect statistically significant increases in adverse event report rates associated with vaccination campaigns. This includes both single vaccine campaigns and campaigns in which the administration of more than one vaccine is undertaken. If the x index denotes occurrences in the group of a given event after immunizations and lastly N vaccinations performed prior to M, and the o index denotes occurrences among the group of N, the relative risk is calculated as follows: Relative Risk (RR) = (a/x)/(b/y), with two equations having the following forms: lg(RR) = lg(a/b) – lg(x/y) and lg(u) = lg(r) + lg(v), where u, r, and v are actuaries of receiving incident events prior to and following immunization campaigns, respectively.

Reduction in HPV-Related Cancers

The HPV vaccine was developed to prevent precancerous lesions associated with HPV, but it was anticipated that vaccination of girls aged 9 to 14 would lead to reductions in cervical, vulvar, and vaginal cancers within 30 years. Studies have shown dramatic declines in genital warts

Research Article doi: 10.18081/2333-5106/014-06/136-146

and low-grade cervical lesions in females and males following vaccination, but many face long-term questions about the public health impact of the vaccine on high-grade HPV-related cancers.

In the US, the cervical cancer incidence rate in 1975 was about 15.4 per 100,000, and the death rate of 5.7 was unchanged for 30 years, expected to rise in the 21st century. Because HPV vaccination was expected to be implemented in the early 21st century, cervical cancer incidence and death rates were projected to increase in the absence of vaccination.

In 2012, the incidence rate of cervical cancer in US females was 6.6 per 100,000, and the death rate of 2.4 was markedly lower than projected. Among white females, the cervical cancer incidence rate fell from 13.8 in 2007 to 7.1 per 100,000 in 2012. This is remarkable because vaccination was expected to prevent cervical cancer after a lag of 30 years.

Meanwhile, the death rate of cervical cancer among white females fell from 4.6 in 2007 to 2.2 per 100,000 in 2012. This is remarkable because cancer death rates were expected to rise annually as the population aged, but instead, death rates have fallen among the racially homogeneous cohort of white females.

The declines in cervical cancer incidence and death rates in 21st century America surprised international experts and called for the need to investigate a possible public health impact of the HPV vaccine on high-grade cervical cancer and death rates in both white and black females. Following the post-HPV vaccine decline in genital warts in girls, scientists reported declines in low-grade cervical lesions in vaccinated girls followed by declines in low-grade anal lesions and genital warts in vaccinated males. However, the question of whether the post-vaccination decline in health services utilized for low-grade cervical screening in vaccinated girls was related to HPV vaccination remains.

Conclusion

In conclusion, worldwide research and surveillance have demonstrated that the risk of serious adverse events is exceedingly low. HPV is a widely spread sexually transmitted virus that can lead to some cancers. Gardasil is a vaccine that protects against the types of HPV that are responsible for the majority of HPV-related disease and cancer. In the U.S., the HPV vaccine Gardasil is given as a series of three shots over a six-month period. The current recommendation is that both girls and boys receive the vaccine between the ages of 11 and 12. Despite being safe and effective, HPV vaccination rates across the United States are low compared to other routine vaccinations for adolescents.

Funding

No funding was received.

Competing interests

The authors declare no conflict of interest.

Research Article doi: 10.18081/2333-5106/014-06/136-146

Ethics Statement

Not applicable.

Authors' contributions

All authors shared in the conception and design and interpretation of data, drafting of the manuscript and critical revision of the case study for intellectual content and final approval of the version to be published. All authors read and approved the final manuscript.

Open access

References

1. Cervantes J, Lema C, Hurtado L, Andrade R, Quiroga G, Garcia G, et al. Prevalence of human papillomavirus infection in rural villages of the Bolivian Amazon. Rev Inst Med Trop São Paulo. 2003;45(3):131–135.
2. Donegan K, Beau-Lejdstrom R, King B, Seabroke S, Thomson A, Bryan P. Bivalent human papillomavirus vaccine and the risk of fatigue syndromes in girls in the UK. Vaccine. 2013;31(43):4961–4967.
3. FUTURE II study group Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med. 2007;356:1915–1927.
4. Tanaka H, Fujita Y, Takenaka Y, et al. Japanese clinical guidelines for juvenile orthostatic dysregulation version 1. Pediatr Int. 2009;51:169–179.
5. Okubo S. Digital plethysmogram. In: Kanai M, editor. Manual of clinical and laboratory medicine. 31. Tokyo: Kanehara Publishing Inc.; 1998. pp. 1546–1547.
6. Bruehl S, Harden RN, Galer BS, et al. Extensive validation of IASP diagnostic criteria for complex regional pain syndrome and proposed research diagnostic criteria. Pain. 1999;81:147–154.
7. Shoenfeld Y, Agmon-Levin N. ASIA-autoimmune/inflammatory syndrome induced by adjuvants. J Autoimmun. 2011;36:4-8.
8. Gisselquist DP. Estimating HIV-1 transmission efficiency through unsafe medical injections. Int J STD AIDS. 2002;13:152–159.
9. Wilder RT. Management of pediatric patients with complex regional pain syndrome. Clin J Pain. 2006;22:443–448.

Research Article doi: 10.18081/2333-5106/014-06/136-146

10. Cervantes J, Lema C, Hurtado L, et al. Prevalence of human papillomavirus infection in rural villages of the Bolivian Amazon. Rev Inst Med Trop São Paulo. 2003;45(3):131–135.
11. Cervantes JL. Multiple human papillomavirus infection: don't forget the genetic background. J Infect Dis. 2011;204(11):1816–1817.
12. Goldenberg DL. Diagnosis and differential diagnosis of fibromyalgia. Am J Med. 2009;122(Suppl. 12):S14-S21.
13. Moro PL, Zheteyeva Y, Lewis P, et al. Safety of quadrivalent human papillomavirus vaccine (Gardasil) in pregnancy: adverse events among non-manufacturer reports in the Vaccine Adverse Event Reporting System 2006-2013. Vaccine. 2015;33(4):519–522.
14. Soldevilla HF, Briones SF, Navarra SV. Systemic lupus erythematosus following HPV immunization or infection? Lupus. 2012;21(2):158–161.
15. Richards S, Chalkiadis, Lakshman R, Buttery JP, Crawford N.W. Complex regional pain syndrome following immunization. Arch. Dis. Child. 2012;97:913–915.
16. Corona Gutierrez CM, Tinoco A, Navarro T, et al. Therapeutic vaccination with MVA E2 can eliminate precancerous lesions (CIN 1, CIN 2, and CIN 3) associated with infection by oncogenic human papillomavirus. Hum Gene Ther 2004;15:421-31
17. Trimble CL, Peng S, Thoburn C, Kos F, Wu TC. Naturally occurring systemic immune responses to HPV antigens do not predict regression of CIN2/3. Cancer Immunol Immunother 2010;59:799-803.
18. Steele JC, Mann CH, Rookes S, Rollason T, et al. T-cell responses to human papillomavirus type 16 among women with different grades of cervical neoplasia. Br J Cancer 2005; 93:248-59.
19. Nagaraj S, Gupta K, Pisarev V, et al. Altered recognition of antigen is a mechanism of CD8+ T cell tolerance in cancer. Nat Med 2007;13:828-35.
20. Curiel TJ, Coukos G, Zou L, et al. Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. Nat Med 2004.
21. Bais AG, Beckmann I, Lindemans J, Ewing PC, Meijer CJ, Snijders PJ, Helmerhorst TJ. A shift to a peripheral Th2-type cytokine pattern during the carcinogenesis of cervical cancer becomes manifest in CIN III lesions. J Clin Pathol 2005;58:1096-100.
22. Kanodia S, Fahey LM, Kast WM. Mechanisms used by human papillomaviruses to escape the host immune response. Curr Cancer Drug Targets 2007; 7:79-89; PMID:17305480.
23. Fahey LM, Raff AB, Da Silva DM, Kast WM. Reversal of human papillomavirus-specific T cell immune suppression through TLR agonist treatment of Langerhans cells exposed to human papillomavirus type 16. J Immunol 2009; 82:2919-28.

24. Domingos-Pereira S, Decrausaz L, Derre L, et al. Intravaginal TLR agonists increase local vaccine-specific CD8 T cells and human papillomavirus-associated genital-tumor regression in mice. Mucosal Immunol 2013;6:393-404.
25. Derre L, Rivals JP, Jandus C, et al. BTLA mediates inhibition of human tumor-specific CD8+ T cells that can be partially reversed by vaccination. J Clin Invest 2010; 120:157-67.
26. Blank C, Mackensen A. Contribution of the PD-L1/PD-1 pathway to T-cell exhaustion: an update on implications for chronic infections and tumor evasion. Cancer Immunol Immunother 2007; 56:739-45.
27. Ukpo OC, Thorstad WL, Lewis JS Jr. B7-H1 expression model for immune evasion in human papillomavirus-related oropharyngeal squamous cell carcinoma. Head Neck Pathol 2013;7:113-21.
28. Scholten KB, Schreurs MW, Ruizendaal JJ, et al. Preservation and redirection of HPV16E7-specific T cell receptors for immunotherapy of cervical cancer. Clinical Immunology 2005;114:119-29.
29. Santin AD, Bellone S, Palmieri M, et al. HPV16/18 E7-pulsed dendritic cell vaccination in cervical cancer patients with recurrent disease refractory to standard treatment modalities. Gynecol Oncol 2006;100:469-78.
30. Garcia F, Petry KU, Muderspach L, et al. ZYC101a for treatment of high-grade cervical intraepithelial neoplasia: a randomized controlled trial. Obstet Gynecol 2004;103:317-26.
31. Gomez-Gutierrez JG, Elpek KG, Montes de Oca-Luna R, Shirwan H, Sam Zhou H, McMasters KM. Vaccination with an adenoviral vector expressing calreticulin-human papillomavirus 16 E7 fusion protein eradicates E7 expressing established tumors in mice. Cancer Immunol Immunother 2007;56:997-1007.

American Journal of BioMedicine
Journal Abbreviation: AJBM
ISSN: 2333-5106 (Online)
DOI: 10.18081/issn.2333-5106
Publisher: BM-Publisher
Email: editor@ajbm.net