

# ISSUE BRIEF



## **The Cervical Cancer Vaccine: What Everyone Should Know and What the Future Holds**

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By Diana Zuckerman, Ph.D., Brandel France de Bravo, MPH, Janet A. Phoenix, MD, MPH

The first cancer vaccine, Gardasil, was approved by the Food and Drug Administration (FDA) in June 2006. Gardasil is approved to protect girls and women, ages 9 through 26, from the two types of Human Papillomavirus (HPV) infection that are responsible for most cervical cancer cases. It has very limited effectiveness, however, against other types of HPV that cause approximately 30% of cervical cancers. For that reason, girls and women who are vaccinated with Gardasil will still need regular Pap smears to detect cervical cancer in its early stages when treatment is most effective.

HPV is the name for a group of viruses that cause cervical cancer, genital warts and several other diseases.<sup>1</sup> There are more than 120 types of HPV, and as many as 40 of them are spread through sexual contact, affecting the genital areas of men and women.<sup>2</sup> Although most types of HPV do not increase the risk of cancer, at least 15 of the 40 types spread by sexual contact have the potential to cause cancers in male or female genitals, the anus, or the throat area.<sup>3</sup> Two of these—HPV 16 and HPV 18—are responsible for approximately 70% of all cases of cervical cancer. Gardasil offers

protection against infections caused by both of these types. The vaccine also provides protection against HPV types 6 and 11, which cause approximately 90% of all cases of genital warts, but do not cause cancer.<sup>1</sup>

HPV is especially dangerous because many of the approximately 6 million people who are infected with genital HPV each year in the United States have no symptoms and therefore do not even know that they are infected. The good news is that in 90% of cases, HPV clears up on its own within 2 years, and often much sooner.<sup>4</sup> Although most HPV infections are short-term, women with persistent infections that last several years are at higher risk for developing cervical cancer.<sup>4</sup> Not all HPV causes cancer, but 99% of cervical cancer can be traced to infection with a strain of HPV.<sup>5</sup> In 2008, approximately 11,000 women in the U.S. were diagnosed with cervical cancer, and an estimated 3,800 women died from cervical cancer, which accounts for less than 1% of all cancer deaths in the U.S.<sup>6</sup> Worldwide, however, cervical cancer is the second most common cancer in women and the third most important cancer in terms of deaths, killing approximately 300,000 women each year.<sup>7</sup>

Public health officials in the U.S. encourage women to have a Pap smear at least every 3 years beginning at age 21, or when they become sexually active. Using Pap smears to detect cervical cancer or precancerous lesions has significantly decreased the number of deaths from cervical cancer. According to the Centers for Disease Control and Prevention (CDC), U.S. deaths from cervical cancer are more likely among women who are uninsured or underinsured. More than half of all U.S. women diagnosed with cervical cancer report never having had a Pap smear or not having one in the past five years.<sup>8</sup>

All women still need regular Pap smears, whether or not they are vaccinated with Gardasil, and whether or not Gardasil remains effective for a woman's entire life. Approximately 30% of cervical cancers are not linked to the HPV types 16 and 18 that the vaccine protects against. It is important to note that cervical cancer has a long lag time between exposure to HPV and the onset of disease, so women may incorrectly assume they are no longer at risk because they are not sexually active or have been in a long-term monogamous relationship. Unfortunately, those women may still be at risk because of previous exposure.

While HPV can cause penile cancer in men, and anal cancer in men and women, these cancers are much rarer than cervical cancer. About 1,700 men a year in the United States are diagnosed with penile (800 cases per year) or anal cancer (900 cases per year), with gay men, bisexual men and men with HIV/AIDS at much higher risk.<sup>2, 9, 10</sup>

### **Gardasil: The Only HPV Vaccine Available in the U.S.**

Gardasil is administered in three doses over a six-month period. The vaccine data thus far are short-term, and Merck states very

clearly on the home page of its Gardasil website ([www.Gardasil.com](http://www.Gardasil.com)), although not in its television ads: "The duration of protection of Gardasil has not been established." Several clinical trials of varying length have been carried out, but none for 10 years or longer, and we still cannot be certain whether the immunity to HPV triggered by Gardasil will last for more than a few years. Because cancers take so long to develop, we will not know the true impact of Gardasil on cervical cancer for several decades. What we do know is that Gardasil provides short-term protection against various strains of HPV (those targeted by the vaccine and one other high risk type) and certain kinds of lesions known to be precursors of cervical cancer. We know this from clinical trials in which women ages 16 to 23 were observed for an average of 38 months to 4.5 years after having completed all three doses of the vaccine.<sup>11,12,13,14</sup>

Will Gardasil need regular booster shots to provide long-term protection? According to the FDA, "It is not clear if and when a booster dose would be required to maintain an immune response and expected efficacy, since at this time, the duration of protective immune response has not been established."<sup>15 (page 25)</sup> Merck has provided the FDA with only one five-year study of women vaccinated with Gardasil, and all the women in the study were given a fourth dose of vaccine at 60 months.<sup>12</sup> That fourth dose increased the women's antibodies to HPV back to the higher levels they had after they were first vaccinated. Merck referred to the 4<sup>th</sup> shot as a "challenge dose, not a booster shot. Since all the women followed for five years received the 4<sup>th</sup> dose, and since the study was stopped one month later, it is not possible to study the impact of this booster by comparing new HPV lesion development in women who had the booster to those who did not. Since the study was stopped, it will not be possible to determine how long the

booster shot is effective, and whether or how often subsequent booster shots will be needed to maintain the vaccine's efficacy.<sup>12</sup>

Although they did not call it a booster shot, Merck's decision to provide a 4<sup>th</sup> vaccine shot to all vaccinated women in their 5-year study is consistent with research indicating that Gardasil's protection against one of the two cancer-causing strains of HPV may diminish considerably over time. By administering the 4<sup>th</sup> shot, Merck made it impossible to determine what percentage of women are protected against any of the HPV strains after five years without a booster. In another study, however, after only three years one woman developed a grade 1 cervical lesion caused by HPV 18.<sup>15</sup> (page 172) Although grade 1 lesions are not considered dangerous, this suggests that the woman may no longer have been protected by the vaccine.

The questions about whether a booster dose is needed, and when, and how many more years of protection it would offer are urgent ones—for vaccinated girls and women who believe themselves protected, and for health officials who need to budget for the cost of the vaccine. Gardasil is the most expensive vaccine to have ever been recommended for school-age children. The vaccine manufacturer charges \$120 for each dose, and the total cost per patient for the initial 3-shot regimen ranges from \$400-\$1,000. The high cost of the vaccine and the unknowns about the cost and frequency of booster shots raise concerns that uninsured women and less affluent women will not be able to afford continued vaccine protection against HPV and cervical cancer as adults, even if the vaccine is paid for when they are children. An additional concern is that vaccinated women might misunderstand the amount of protection from the vaccine and therefore fail to seek regular Pap screening. Uninsured and low-income women are especially of concern because they are least

likely to get regular Pap smears and therefore are the most likely to die of cervical cancer. If a woman receives an HPV vaccine (with or without boosters) lasting less than 15 years, and doesn't continue to receive effective booster shots, then vaccinating at a very young age is likely to delay cervical cancer for several years but not prevent it.<sup>16</sup>

Ten-year trials are being carried out with young adolescents in Finland and Sweden, but these will study the impact of the vaccine on lesions and disease, with less emphasis on monitoring antibody titers (immunity). Although lesions and disease are the most important measure of vaccine success, studies that do not also regularly measure antibodies are unlikely to answer questions about the need for boosters for at least 10 years, and possibly much longer.

## **National Recommendations**

On June 29, 2006, the CDC's Advisory Committee on Immunization Practices (ACIP) recommended that Gardasil be given routinely to all 11-12 year old girls. The recommendation was based on less than two years of efficacy, safety and immunogenicity data provided to the FDA from clinical trials with 16-23 year-olds, combined with safety and immunity studies in 9-15 year old girls.<sup>17</sup>

Why was Gardasil recommended for girls 9-15 years old without efficacy data based on lesions? These younger girls developed similar antibody titers to the 16-23 year olds, who were protected from lesions, so the assumption was that the vaccine would be equally effective. However, rather than recommending the vaccine for 9 year olds, the ACIP recommended it for 11-12 year olds as a means of increasing contact with pre-teens, all of whom need preventive counseling and screening on issues of

national concern such as obesity, depression and the consequences of unprotected sex. According to the American Academy of Pediatrics, pediatricians have generally been unsuccessful at persuading parents to bring in their 11-12 year olds for preventive counseling and screening for risky health behaviors. It was felt that the HPV vaccine might be the incentive parents needed to bring in their daughters for this more inclusive preventive physician visit.<sup>18, 19</sup>

The U.S. Department of Health and Human Services accepted the Committee's recommendation and it is estimated that 85-89% of children with health insurance are covered for Gardasil and other routine vaccinations.<sup>20, 21, 22</sup> The CDC Committee has also recommended that the HPV vaccine be included in the Vaccines for Children (VFC) Program, the federal program which provides free vaccinations to children 18 years of age and under who are uninsured, on Medicaid, protected by the Indian Health Services Act, or underinsured patients at Federally Qualified Health Centers and Rural Health Clinics.<sup>23</sup> Approximately 41% of all childhood vaccines in the United States are purchased by and administered through the VFC Program.<sup>24</sup> However, the CDC recommendation does not include a booster shot, and even if it did, once the girls were older than 18 years, the VFC Program would not cover the cost of Gardasil or a booster.

The high cost of the vaccine is important to insurance companies and state health officials. Insurance companies in New Hampshire opted to contribute a lump sum to state health funds for VFC rather than reimburse policy-holders for Gardasil and other vaccines required of 11-18 year olds.<sup>25</sup> Yet even with monies from private insurance companies, state health departments will likely not have enough money to purchase 3 doses of Gardasil for every 9-18 year old in their state who

qualifies under VFC. In 2007, New Hampshire planned to spend \$4.9 million-28% of the state immunization budget-on Gardasil alone.<sup>25</sup>

### **At What Age is Gardasil Most Effective?**

The data that Merck presented to the FDA in 2006 indicated that Gardasil would not be effective against strains of HPV that the women were currently infected with at the time of vaccination. This finding has often been misunderstood. For example, the CDC web site says: "Ideally, girls/women should get this vaccine before their first sexual contact when they could be exposed to HPV. This is because the vaccine prevents disease in girls/women who have not previously acquired one or more types of HPV prevented by the vaccine. It does not work as well for those who were exposed to the virus before getting the vaccine...The vaccine will not treat existing infections." This statement fails to clearly distinguish between active HPV infections (which the vaccine does not cure) and previous HPV infections (which apparently do not interfere with the vaccine's effectiveness). This is an important distinction because the CDC's research shows that approximately 10% of all children have been exposed to HPV 16, the most cancerous of the HPV types, in their first decade of life.<sup>26, 27</sup> In addition, the Merck trials showed that among sexually active 16-23 year old females, 20% had been exposed to one or more of the four HPV types covered by the vaccine, but only 15% had a current infection with one or more of those four HPV types.

Since HPV exposure can occur even in the first 10 years of life, there is no age during which Gardasil will always be effective for everyone. An ideal age to give Gardasil cannot be predicted by youth or previous sexual exposure. Since HPV can go away by itself, it is not clear from their statements whether the CDC believes that women

previously exposed to HPV at any time will benefit less from the vaccine, or only those infected at the time they are vaccinated.

However, when longer-term data became available in 2008, it became clear that most teenagers and women who were vaccinated after being previously exposed to HPV have even more antibodies than those who were vaccinated before they became sexually active.<sup>13</sup> Only the small proportion of girls and women with active HPV 6, 11, 16 or 18 infections at the time of vaccination do not benefit from Gardasil in the 3-4 years following the vaccination.

Based on the data presented in 2006, Merck concluded that the vaccine should be prescribed to girls *before* they become sexually active. Since CDC routinely assumes that vaccines provide life-time protection, vaccinating young girls was also considered the most cost-effective strategy, costing \$43,600 for each healthy year of life saved.<sup>28</sup> However, given that Merck administered a fourth dose of vaccine at 60 months, it appears that Merck believes a booster is necessary, although the company has not said so in any publicly available written materials. A cost effectiveness study published in the *New England Journal of Medicine* in 2008 concluded that if the vaccine provided protection against HPV for only ten years, then vaccinating preadolescent girls would only provide a "2% marginal improvement in the reduction in the risk of cervical cancer as compared with screening alone." Moreover, it would cost \$144,100 for each healthy year of life saved, instead of the \$43,600 estimated for a vaccine providing life-long protection.<sup>28</sup> Most researchers believe that interventions costing more than \$50,000 per quality-adjusted year of life (QALY) saved are not cost-effective, while others use a higher ceiling of \$100,000.

The discrepancy between Merck's initial claims that the vaccine was most effective for young girls not yet exposed to HPV, and new data indicating the vaccine may be *equally or more effective*, rather than less effective, for sexually active teenagers and young women has important policy implications. These data, therefore, deserve close scrutiny.

Antibody titers indicate immunity, and for any vaccine these tend to decrease over time. What is not known is how high titers have to be in order for a person to be protected from a given disease. Merck's researchers measured titers to HPV 16 and 18 in girls 9-12 years old 30 months after vaccinating them. For young women between the ages of 16-26, Merck's researchers measured titers at 38 to 50 months. Even though the older group's titers were measured later and would therefore be expected to be lower, the 16-26 year old women who had already been exposed to HPV 16 or 18, and had not had any cervical lesions develop from the infections, had almost as high or a higher immune response to the vaccine as the pre-teens.<sup>15</sup>

Overall, the latest research suggests that, contrary to what has been stated by the CDC and Merck, sexually active women—even those exposed to HPV in the past—will benefit from the vaccine, because most HPV goes away by itself rather than developing into cervical cancer.<sup>29</sup> A French researcher recently presented results of a study on 17,000 women and found that Gardasil prevented cervical lesions among women with previous HPV exposure at nearly the same rate as it did among women with no previous HPV exposure: 40 lesions per 10,000 women as compared with 30 lesions per 10,000 women.<sup>30</sup>

## **Does the Vaccine Provide More Protection than the Virus?**

The purpose of any vaccine is to provide more protection against the health risks of the virus than would occur naturally if the person was exposed to the virus. Does Gardasil achieve that goal?

Just three years after being vaccinated with Gardasil, one-third of women had lost all their antibodies to HPV 18 while the rest had the same level of titers as girls and women exposed to the virus through sexual contact but never vaccinated.<sup>12</sup> While some viruses, such as Hepatitis B, do not require that the vaccine against them stimulate titers higher than natural infection, there is no proof that this would be true of HPV. Researchers are divided on this issue. Those who believe that only low amounts of HPV antibodies are necessary to prevent infection, point to the example of the Hepatitis B vaccine, which gives direct stimulation to the memory immune system via the blood stream.<sup>i</sup> Unlike Hepatitis B, however, HPV is an epithelial infection, which means it actively avoids the immune system, causing very little stimulation of the memory response.<sup>ii</sup> Therefore, more research is needed to determine whether or not the lower levels of antibodies indicate that protection against some strains of HPV diminishes after a few years.

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<sup>i</sup> The direct stimulation to the memory immune system requires low to no detectable circulating Hepatitis B antibodies for protection, instead relying on the memory response to make antibodies, which can then neutralize the Hepatitis B floating in the blood. But HPV is not a blood-borne virus, and does not stimulate memory responses as quickly as Hepatitis B can.

<sup>ii</sup> HPV infections require very high circulating levels of antibodies immediately available to neutralize the new HPV infection. Natural HPV infection may stimulate a small memory response to replenish the circulating supply of antibodies.

All experts agree that natural exposure to HPV can cause cancer and therefore does not prevent people from possibly developing cervical cancer. That is the reason why the similarity of titers between vaccinated women and those naturally exposed to HPV is raising questions about the long-term efficacy of the vaccine. Those doubts are exacerbated by Merck's decision to give a 4<sup>th</sup> shot after five years to all the vaccinated girls and women in their follow-up study.

Given these concerns, research is needed to determine if a booster given at a particular time is needed to improve Gardasil's protection, and if so, how long the booster would be effective against which strains of HPV.

## **At What Age Should Girls be Vaccinated?**

Is it a good idea to vaccinate girls as young as 12? Based on the incorrect information about the ineffectiveness of the vaccine for sexually active teenagers, several states are considering laws requiring HPV vaccines for school attendance. In Virginia and Washington, D.C., for example, all girls entering sixth grade in the fall of 2009 will be required to be vaccinated against HPV. While Gardasil may be safe for girls as young as 12, we do not yet have enough data on how effective it is or how long it lasts to justify this policy, particularly given the high cost of the vaccine to working class and middle class parents and to government health programs for the poor. Gardasil's safety and antibody response to the vaccine was tested on girls as young as 9 and 10, but the impact on lesions or disease was not studied in girls under 16. Given the data indicating a lowering of antibodies against HPV 18, a major cause of cervical cancer, many girls vaccinated with Gardasil at age 12 could possibly lose much of their

immunity against HPV 18 just as they are becoming more sexually active at ages 16 or 17.

If that is true, scarce public resources could be better spent to administer the vaccine at age 14, 15, or 16, or to increase the availability of Pap smears for underinsured or low-income women.

Another option is to delay making mandatory policy decisions about the vaccine until Gardasil is compared to the other HPV vaccine, Cervarix, made by Glaxo Smith Kline. Although Cervarix was approved in at least 66 countries in Europe and Australia, FDA has required longer-term studies of Cervarix than they required of Gardasil, and FDA approval has been delayed while those studies are completed. Published studies suggest that Cervarix may trigger a greater immune response than Gardasil, and may provide protections against both HPV 18 and 16 for at least 6.4 years.<sup>31</sup> Comparisons of the two vaccines would enable policy makers to make appropriate decisions regarding whether to specifically require one of the vaccines or give parents a choice. However, neither parents nor policy makers can make an informed choice until FDA requires similar long-term research on effectiveness in preventing lesions or disease for both products; even then, choice is not possible unless both products are approved by the FDA.

As with any sexually transmitted disease, all it takes is exposure to one infected partner to acquire HPV. However, the chances of HPV and cervical cancer increase with the number of sexual partners, and the number of sexual partners of their sexual partners. Research is now underway to evaluate the effectiveness of Gardasil among women 27 to 45, and also in boys and men.

## Vaccination Effects and Safety

As of August 2008, more than 20 million doses of Gardasil had been distributed in the U.S. and there were 10,326 reports registered through the CDC's Vaccine Adverse Event Reporting System (VAERS).<sup>32</sup> Minor side effects, such as pain or tenderness at the injection site, are quite common. Other reactions, such as headache, fever, nausea, and dizziness were, at the time of approval, no more likely after receiving the vaccine than after receiving a placebo.<sup>17</sup> The most common side-effect observed since Gardasil became available to the public-fainting after receiving the vaccine-is being dealt with by warning health providers to keep patients under observation for 15 minutes after giving the shot.

Serious but rare side effects such as Guillain-Barré Syndrome (GBS), which causes muscle weakness, have been reported, however. According to the CDC, cases of GBS following administration of Gardasil do not represent a statistically significant increased risk, even though 9 of the 13 reported cases of GBS occurred during a biologically plausible time frame.<sup>33</sup> <sup>34</sup> Therefore, more research is needed to determine if girls or women vaccinated with Gardasil are at an increased risk for GBS or related symptoms. Similarly, in Australia, the rate of anaphylaxis shock after Gardasil injection has been reported as 2.6 per 100,000 doses.<sup>35</sup>

Like any public health intervention, a vaccine's risks must be weighed against its benefits. This is why it is so important to determine the vaccine's efficacy and how long it lasts. If the vaccine is offering minimal protection or instilling a false sense of immunity, almost any risk or adverse reaction becomes unacceptable.

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