The Human Papillomavirus Vaccination Debate

By

Samuel Bell

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Lori A. Evarts, MPH PMP CPH

Michael Rosenberg, MD-MPH

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Abstract

The overwhelming majority of cervical cancer deaths are caused by a sexually-transmitted virus: the human papillomavirus, or HPV (Walboomers et al., 1999). According to the Centers for Disease Control and Prevention, about 4,000 American women die from it each year. A vaccine would seem a welcome tool in the fight against this deadly disease. However, the introduction of the first HPV vaccine in the United States in 2006 was met by controversy and public opposition (Schwartz, Caplan, Faden, & Sugarman, 2007). This negative reaction to the vaccine was centered on attempts by its manufacturer, Merck & Co., Inc., to make it a required childhood vaccine for school-aged girls. The attempt to create an HPV vaccination mandate largely failed. The reasons for the failure were complex and arose in the context of political opposition, public skepticism about vaccines, unresolved scientific questions, and issues of cost.
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<tbody>
<tr>
<td>ACIP</td>
<td>Advisory Committee on Immunization Practices</td>
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<td>CBER</td>
<td>Center for Biologics Evaluation and Research</td>
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<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
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<td>DNA</td>
<td>Deoxyribonucleic acid</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>HHS</td>
<td>United States Department of Health and Human Services</td>
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<td>HPV</td>
<td>Human papillomavirus</td>
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<td>NHANES</td>
<td>National Health and Nutrition Examination Survey</td>
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<td>NCSL</td>
<td>National Conference of State Legislatures</td>
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<td>n.d.</td>
<td>No date</td>
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<td>NVIC</td>
<td>National Vaccine Information Center</td>
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<td>STD</td>
<td>Sexually transmitted disease</td>
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<tr>
<td>VFC</td>
<td>Vaccines for Children</td>
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<td>VICP</td>
<td>Vaccine Injury Compensation Program</td>
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The Human Papillomavirus Threat

Across the globe each year, more than 500,000 women develop cervical cancer, and close to 300,000 women die from it (Jemal, Bray, Center, Ferlay, Ward, & Forman, 2011). Within the United States in 2007, 12,280 women were diagnosed with cervical cancer and 4,021 women were killed by it (Centers for Disease Control, n.d., Cancers: Cervical Cancer Statistics). Almost all of these deaths - more than 99% - were caused by a sexually-transmitted virus: the human papillomavirus, or HPV (Walboomers et al., 1999). This common virus causes other health problems, some of them fatal, among both men and women. HPV is now thought to be the cause of about 85% of anal cancers, 70% of vaginal cancers, 40% of vulvar cancers, 40% of penile cancers, 35% of throat cancers, and 25% of oral cancers (De Vuyst, Clifford, Nascimento, Madeleine, & Franceschi, 2009; Parkin & Bray, 2006; Kreimer, Clifford, Boyle, & Franceschi, 2005). In addition to causing cancers, HPV causes genital warts, which are not generally life-threatening (since they are usually caused by different types of the virus than those associated with cancers) but can have a devastating impact on people's quality of life (National Cancer Institute, 2010).

Given these frightening statistics, one might assume that a vaccine that could prevent many of these infections and cancers would be universally welcomed. However, the 2006 introduction of the first HPV vaccine in the United States, Gardasil (developed by Merck & Co., Inc.), was immediately met by controversy and public opposition (Schwartz, Caplan, Faden, & Sugarman, 2007). This negative reaction to the vaccine was centered on attempts to make it a required childhood vaccine for school-aged girls. The reasons for the reaction are complex and involve the intersection of children, sex, politics, economics, religion, public understanding of vaccine efficacy and safety, and the role of government interventions for the public good.
This paper examines the context within which the Gardasil HPV vaccine was developed, the way in which it was introduced to the public, the attempt by the Merck to have it become a state-mandated childhood vaccine, and the opposition that the proposed mandate provoked. The system by which new vaccines become recommended for general use in children, and Gardasil's encounter with this system, is also described. The factors that led to the general failure of a new mandate for HPV vaccination are discussed, partly through a comparison with the previous successful development of mandates for hepatitis B vaccinations. A timeline of key events concerning the development and launch of Gardasil is provided on pages 24-25.

**The Development and Approval of an HPV Vaccine**

In 1842, the Italian doctor Domenico Rigoni-Stern noticed that cervical cancer was much less common among virgins and nuns than among women who had been married; this was the first evidence that the cancer could be connected to a sexually transmitted disease. By the early 1980s, evidence began to indicate that there was a link between cervical cancer and the human papillomavirus (McNeil, 2006). Evidence of the link was developed by Harald zur Hausen, a German scientist who shared the 2008 Nobel Prize in Medicine for his work (Altman, 2008). Dr. zur Hausen first suggested the link between HPV and cervical cancer in 1976 and, through further research, more firmly identified a relationship between cervical cancer and HPV types 16 and 18 in 1983 (zur Hausen, 1976; Dürst, Gissmann, Ikenberg, & zur Hausen, 1983). Before zur Hausen's work, strong evidence was lacking for a causal link between cancer and viruses.

The link between a virus and cervical cancer opened the possibility of developing a cancer vaccine. The basic science behind such a vaccine for cervical cancer was developed by Douglas R. Lowy and John T. Schiller, scientists at the National Cancer Institute’s Laboratory of Cellular Oncology. They discovered that an immune response could be provoked by the proteins
in the outer shell of the human papillomavirus (Barr, 2007). This discovery indicated that a relatively safe vaccine could be developed that would not require exposure to any form of active virus.

The basic principles developed by Lowry and Schiller set off a race to develop a marketable vaccine. The first new drug approval application in the United States for an HPV vaccine was filed with the FDA’s Center for Biologics Evaluation and Research (CBER) by Merck at the end of 2005. On May 18, 2006, CBER’s Vaccines and Related Biological Products Advisory Committee met in a public session to review the vaccine and receive input from interested parties. The panel recommended approval of the vaccine (Bridges, 2006). The FDA approved the vaccine on June 8, 2006.

As stated in FDA’s approved product information, the Merck vaccine is a quadrivalent vaccine that provides immunity against HPV types 6, 11, 16 and 18. Out of more than 100 types of HPV, researchers linked about 70% of cervical cancer cases to types 16 and 18, and about 90% of genital wart cases to types 6 and 11. Although the genital wart strains generally do not cause cervical cancer, they were added to the vaccine as an additional incentive for males to get vaccinated, since males can be carriers of the cancer-causing strains. However, the initial marketing approval sought by Merck for the vaccine did not include males. The original Merck application and FDA-approved indication in 2006 allowed Gardasil to be administered to females from the ages of 9 to 26 (United States Food and Drug Administration [FDA], n.d., Gardasil).

The target population for the new HPV vaccine was potentially vast. According to data from the National Health and Nutrition Examination Survey (NHANES) that was collected in 2003-2004 (prior to the marketing approval of the first HPV vaccine):
Prevalence of HPV DNA in a representative sample of US females aged 14 to 59 years was 26.8%, with the highest prevalence (44.8%) among women aged 20 to 24 years. The overall prevalence of HPV among females aged 14 to 24 years was 33.8%. This prevalence corresponds with 7.5 million females with HPV infection. The prevalence of high-risk HPV types 16 and 18 were 1.5% (95% CI, 0.9%-2.6%) and 0.8% (95% CI, 0.4%-1.5%), respectively. (Dunne, Unger, Sternberg, et al., 2007)

Figure 1: Prevalence of Low-Risk and High-Risk HPV Types Among Females Aged 14 to 59 Years, NHANES 2003-2004

Error bars indicate 95% confidence intervals. Both low-risk and high-risk HPV types were detected in some females. Low-risk HPV types are defined as HPV type 6, 11, 32, 40, 42, 44, 54, 55, 61, 62, 64, 71, 72, 74, 81, 83, 84, 87, 89, and 91; and high-risk HPV types as HPV type 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73, 82, 85, and IS39 (Dunne, Unger, Sternberg, et al., 2007).

Immunization Recommendations

Following the FDA approval of the vaccine, the next crucial step in establishing the broadly accepted use recommendations for Gardasil was its review by the Advisory Committee on Immunization Practices (ACIP). Organized under the auspices of the U.S. Department of Health and Human Services and the Centers for Disease Control and Prevention (CDC), the ACIP is an advisory panel of fifteen members. This panel is the sole federal government entity with responsibility for developing written recommendations on vaccination practices in the United States (Centers for Disease Control and Prevention [CDC], n.d., Advisory Committee on
Immunization Practices [ACIP]). Although the ACIP cannot set legal mandates for childhood vaccines (which are the responsibility of the states), its recommendations are considered largely authoritative and tend to be followed in establishing vaccination recommendations and requirements for various target groups. ACIP recommendations also determine which vaccinations will be covered by the federally-funded Vaccines for Children (VFC) Program. Administered through Medicaid, this program provides vaccines for free to children who otherwise may not receive them because of cost (CDC, n.d., Vaccines for Children Program [VFC]).

The ACIP met on June 29, 2006 to review Gardasil. By a 13-0 vote (two members abstained due to conflicts of interest), the committee recommended "routine vaccination of females 11-12 years of age with three doses of quadrivalent HPV vaccine. The vaccine series can be initiated in females as young as 9 years of age at the discretion of the provider" (CDC, 2006). This recommendation established the Gardasil vaccination as a recognized standard of care for young girls.

Formation and implementation of HPV vaccination policies in the United States then moved to the state level. The ACIP recommendation of routine HPV vaccination contributed to the question of whether it should be added to the lists of mandated vaccines for school children. Under the powers delegated to the individual states by the U.S. Constitution, states are allowed to pass laws "reasonably related to the promotion and maintenance of the health, safety, morals, and general welfare of the public;” this power has been interpreted by case law to include the power to require vaccinations for communicable diseases (Dowling, 2008). Vaccination mandates vary by state, both in terms of the required vaccines and the exceptions to use that are allowed. Every state has mandated vaccines for school children, but exemptions are allowed. All
states have exemptions for medical reasons. Forty-eight states (all except Mississippi and West Virginia) allow exemptions from vaccinations based on religious belief. Twenty states allow exemptions based on non-religious philosophical beliefs (National Conference of State Legislatures [NCSL], 2010).

Vaccination Marketing and Mandates

Even before receiving FDA approval for Gardasil, Merck began marketing efforts for the new vaccine. Its first step was supporting the "Make the Connection" campaign, which was intended to publicize the connection between HPV and cervical cancer. The campaign distributed bracelet kits and information through a Web site and toll-free number; by January of 2006, several months before marketing approval for Gardasil, Merck had distributed more than 100,000 bracelets. (Merck and Co., Inc., 2006) This effort was followed by the "Tell Someone" campaign, which encouraged women to talk with others about HPV and cervical cancer. Both of these disease awareness campaigns were motivated by Merck's findings that most women were unaware of the HPV-cervical cancer link (Herskovits, 2007). In the two months prior to the FDA approval, Merck ran more than a thousand TV commercials in its awareness campaign (Zimm & Blum, 2006). Then, following the marketing approval in June 2006, Merck launched its direct-to-consumer marketing campaign that included the first advertisements mentioning Gardasil by name. Known as the "One Less" campaign, its commercials features girls making statements such as, "Each year in the U.S., thousands of women learn they have cervical cancer. I could be one less" (Dederer, 2007).

Combined with the direct-to-consumer advertising, Merck began an intense lobbying effort to have Gardasil added to the list of vaccines mandated for children attending public schools (Gardner, 2007). For the vaccine to be maximally effective, it must be administered
before recipients become sexually active. Janet Gilsdorf, MD, a member of the ACIP's HPV Working Group, stated "We decided to focus on 11 and 12 year olds because there's a strong movement afoot to establish adolescent visits [to the doctor] at a time of life when people aren't going to the physician for routine care" (Herskovits, 2007). Therefore, the ACIP recommended that the best time to administer the vaccine is when children are about 11-12 years old, and a school mandate for HPV vaccination would target sixth grade girls.

If HPV vaccination had become mandatory, it would have had two effects that would have benefitted Merck. First, it would have given Merck a virtually guaranteed large market for Gardasil. As the first HPV vaccine to go to market, and as the one that offered protection against the greatest number of HPV types (GlaxoSmithKline's Cervarix, which did not received marketing approval until October 16, 2009, only protects against HPV types 16 and 18), Gardasil was in a good position to become the standard HPV vaccine. Second, if HPV vaccination were to become a mandated childhood vaccine, Merck could receive liability protection for injuries caused by the vaccine under the auspices of the National Childhood Vaccine Injury Act of 1986. This law created the National Vaccine Injury Compensation Program (VICP), which included a provision moving injury lawsuits against vaccine makers from the regular state and federal court systems into "a no-fault alternative to the traditional tort system for resolving vaccine injury claims that provides compensation to people found to be injured by certain vaccines" (United States Department of Health and Human Services [HHS], n.d., VICP). In order for a vaccine to be placed under this program, it needs to be recommended by the ACIP, subjected to a federal excise tax, and approved for the program by the Secretary of Health and Human Services (HHS, n.d., Newly Licensed Vaccines & VICP Coverage).
Merck’s proposal for a school vaccination mandate was supported by a number of other organizations; among the most prominent was Women in Government, which received funding from Merck for some of its lobbying efforts (Women in Government, n.d.; Associated Press, 2007). Other organizations, such as the American Cancer Society, Centers for Disease Control and Prevention, and the American Academy of Pediatrics also supported widespread use of the vaccine, but were wary of supporting a vaccination requirement for school attendance. In 2006-2007, immediately following the FDA approval and ACIP recommendation, 41 states as well as the District of Columbia introduced legislation to mandate, pay for, or provide information to the public about HPV vaccination. Attempts to require use of the vaccine, however, produced a backlash from a number of interest groups and segments of the public.

In September of 2006, Michigan became the first state to introduce proposed legislation for an HPV vaccination mandate (Eggert, 2006). Between the fall of that year and the beginning of 2007 at least 18 states initiated debate on an HPV vaccination mandate, but in the face of controversy a number of states began dropping the proposal (Wyatt, 2007). The biggest public battle over a proposed HPV vaccination mandate, however, arose in Texas. At the beginning of 2007, bills to mandate the vaccine for schoolgirls were under debate in both houses of the Texas legislature (Ackerman, 2007). On February 2, 2007, however, before the bills could become law, Governor Rick Perry issued an executive order requiring girls starting the sixth grade by September 2008 to receive the vaccine (Hoppe, 2007a). Although the order allowed parents to opt out for reasons of religion or conscience, it provoked an immediate and intense backlash. Social conservatives, who had previously been among Perry's supporters, attacked the governor for interfering with parental rights and encouraging sexual permissiveness (Elliott, 2007). Saying that the legislature had not been allowed the opportunity to discuss the mandate or consider its
implications, a state senator announced his intention to introduce legislation to overturn the executive order (Lewis, 2007). Critics quickly pointed out that Perry and a number of state legislators had received campaign donations from Merck, and Perry's former chief of staff had become a lobbyist for the pharmaceutical company (Elliott, Ackerman, & Radcliffe, 2007). Within three months, the Texas legislature passed a bill that overturned Perry's order (Hoppe, 2007b). The action and reaction in Texas brought public attention and scrutiny to Merck's active political role in promoting a vaccine mandate. In the midst of the controversy, the events and revelations in Texas became the final blow to Merck's strategy. Merck retreated from its position and on February 20, 2007, publicly dropped its national campaign to make Gardasil a required vaccine (Pollack & Saul, 2007a).

Some other states, including North Carolina, North Dakota, Utah, and Washington, passed laws requiring the distribution of educational materials on HPV and the vaccine (NCSL, 2011). Ultimately, however, HPV vaccination requirements associated with school attendance only went into effect in Virginia and the District of Columbia, and in both cases broad special exemptions were allowed. While all other vaccines with school mandates only allowed exemptions for medical or religious reasons, the District of Columbia and Virginia both specifically allowed parents to opt their children out of the HPV vaccine for any reason (Stewart, 2008).

**Political Opposition**

Political opposition to the HPV vaccination mandate came from a variety of sources and its roots pre-dated the FDA approval of Gardasil. The movement for abstinence-only sex education was one source of opposition. Some of these critics of a vaccination requirement began airing their concern that the forthcoming HPV vaccine could give a false sense of security
and encourage teenage sexual activity (Stein, 2005). Concerns about high rates of HPV had been used by social conservatives for a number of years prior to the advent of Gardasil as a reason for supporting abstinence-based sex education. Sandy Rios, president of Concerned Women for America, and Robert Knight, a member of the advisory board for the National Abstinence Clearinghouse, declared in a 2002 editorial:

Everyone knows that HIV is fatal. But how many know that at least 5,000 women die yearly in the United States from other sexually transmitted diseases (STDs)? Most cases of cervical cancer are caused by human papillomavirus (HPV), an STD that infects more than 5 million people annually. Condoms are useless against HPV and nearly useless against genital herpes. Despite this, the government is still spending millions of dollars to persuade kids to have 'safe sex' by using condoms. As the epidemic rages, the one bright spot is the success of abstinence programs, which reduce teen sexual activity. (Rios & Knight, 2002)

In the spring of 2005, Bridget Maher, a spokesperson for the Family Research Council, asserted that "Giving the HPV vaccine to young women could be potentially harmful, because they may see it as a license to engage in premarital sex" (MacKenzie, 2005). Reginald Finger, who had served as a medical advisor for the pro-abstinence group Focus on the Family, and was a member of the ACIP appointed under President George W. Bush, stated in late 2005 that "If people begin to market the vaccine or tout the vaccine that this makes adolescent sex safer, then that would undermine the abstinence-only message" (Sheffield, 2005). (Finger, however, ultimately supported the ACIP's vaccination recommendation [CDC, 2006].)

Such sentiments were quickly subjected to intense criticism. As one headline read, "Religious right would kill to stop safe sex" (Traister, 2005). Within this atmosphere, conservative critics soon backtracked, and by the time the vaccine was approved, few organized groups claimed that the vaccine would promote promiscuity (Gibbs, 2006).
Conservative opposition to an HPV vaccination mandate narrowed to claims about parental choice and concerns about the safety of the vaccine. By 2007, the Family Research Council had issued a clarification of its spokesperson's media remarks, and asserted:

*The only public policy measure which we would oppose in promoting the vaccine is an effort to make it mandatory for school attendance. Our reason for that is that it would infringe upon parental rights to decide their own children's medical care, without sufficient public health justification (because HPV is not transmitted through casual contact). To repeat, our opposition to mandatory vaccination is rooted in a concern about parents' rights, not about sexual behavior.*

(Family Research Council, 2007)

Despite the backpedalling by prominent organizations, individual parents often objected to the vaccine based on concerns that the vaccine could encourage sexual activity or raise a topic for which their children were not ready (Wiggins, 2007). In a survey of California parents, the most frequently specified reasons for parents who were unlikely to have their daughters vaccinated were concerns about the impact of the vaccination on the girls' sexual behavior. However, despite the relative frequency of these concerns, only about 7.6% of the parents said they would avoid having their daughters vaccinated because of them (Constantine & Jerman, 2007).

Political criticism of the move to mandate HPV vaccinations was not limited to conservatives. Liberal commentators and organizations also questioned the vaccine. Merck’s aggressiveness in promoting a requirement for the vaccine led to a suspicion that its health claims were motivated by a desire for profits. It was noted, for example, that Merck faced millions in legal fees and payouts over Vioxx, its painkiller that was linked to adverse cardiovascular events (Pollack, & Saul, 2007b). PR Watch, an online publication affiliated with the Center for Media and Democracy, published a lengthy investigation on "The Politics and PR of Cervical Cancer," which concluded:
Ironically, there is serious concern that vaccination may in fact create a false sense of security that will make reliable and effective Pap screening seem less important and cases of HPV infection that develop into cervical cancer more common... While Merck and its partners have been working to reach individuals to convince them of their need for this vaccine, they have also been pursuing an even more fruitful goal. Merck's hope is that most if not all states will mandate a vaccine against HPV as a pre-requisite for school attendance. A mandatory vaccination for more than half of the population is the financial equivalent of the Holy Grail for a pharmaceutical company.  
(Siers-Poisson, 2007)

The nature of the disease and rationale for the vaccine were also generally different from other required vaccines; most other childhood vaccinations are for highly contagious and airborne diseases that can be easily spread within a school context (e.g., measles), but HPV can only be spread by intimate contact. This fact led civil libertarians to question whether the government had sufficient grounds for requiring HPV vaccinations for school attendance (Stewart, 2008). For these critics, expanded government vaccination mandates were part of a slippery slope that threatened to become a form of government overreach.

Others questioned why the vaccine would only be required for girls, ignoring the role of males in the spread of HPV. As one pair of commentators noted, "Issues of fairness arise if young girls are compelled to submit to a new vaccine as a condition of receiving publicly funded education, when boys are not" (Gostin & DeAngelis, 2007).

Vaccine Skepticism

Skepticism about vaccination safety also played a role: Gardasil was introduced at the same time that there had been a growing level of popular skepticism about vaccination in general. For example, although scientific studies have refuted the claim, many people have come to believe that there is a linkage between some vaccines and autism (McNeil, 2009). In 1998, Andrew Wakefield published his now-notorious article alleging a link between some vaccines and the onset of autism in young children (Wakefield, Murch, Anthony, et al., 1998).
By 2000, this allegation had led to Congressional hearings on the issue in the United States, and numerous lawsuits by families of autistic children followed (Hilts, 2000; Vedantam, 2007). A number of follow-up studies questioning Wakefield's results, as well as the retraction of his original article by The Lancet and later accusations of fraud against him, have so far done little to reduce the skepticism about vaccinations that was set in motion (Haris, 2007; Deer, 2011).

There were no allegations that Gardasil was linked to autism. Among other factors, it did not include thimerosal, the mercury-based preservative that was alleged by many to be the root cause of the autism link, and the targeted patient population was past the normal age of autism onset. However, after the autism controversy became public, it contributed to the climate of popular skepticism about vaccinations. Included with this skepticism was a movement among people who felt that vaccinations were in some sense unnatural and that children were better off building natural immunity through exposure to some diseases. For instance, there were claims that some parents deliberately exposed their children to chicken pox rather than (or in addition to) receiving the chicken pox vaccine (Henry, 2005).

One of the most prominent organizations that promoted skepticism about vaccines, the National Vaccine Information Center (NVIC), emphasized concerns about the safety and cost of Gardasil. In a press release, the organization's president was quoted:

GARDASIL safety appears to have been studied in fewer than 2,000 girls aged 9 to 15 years and it is unclear how long they were followed up. [The federal Vaccine Adverse Event Reporting System] is now receiving reports of loss of consciousness, seizures, arthritis and other neurological problems in young girls who have received the shot," said NVIC President Barbara Loe Fisher." At the same time, parents who take their daughters to private pediatricians are going to be shocked to find that they will be paying two to three times the widely publicized $360 cost for the three-dose series. The cost is going to break the pocketbooks of parents and break the banks of both insurance companies and taxpayers, when the reality is that almost all cases of HPV-associated cervical cancer can be prevented with annual pap screening of girls who are sexually active.

(National Vaccine Information Center, 2007)
It should be noted that the NVIC failed to assess the costs of annual Pap tests versus the cost of the vaccine, and they also did not analyze the comparative availability and reliability of Pap tests. Further, the NVIC also did not acknowledge that cervical cancer prevention on the basis of Pap test findings often requires surgical intervention.

**Unresolved Scientific Questions**

A number of scientific questions about Gardasil were still unresolved at the time of its marketing approval. These unresolved issues led some scientists and public health professionals, as well as members of the public at large, to question whether it was appropriate to move swiftly toward a vaccination mandate.

The actual impact of HPV vaccination on cervical cancer rates is unknown. Because an HPV infection can take several decades to develop into cervical cancer, the primary endpoint of Merck's pivotal clinical trials was not cervical cancer, but instead infection with the HPV types covered by the vaccine (Koutsky, Ault, Wheeler, et al., 2002). Although it is almost certain that elimination of infections with HPV types 16 and 18 will reduce the incidence of cervical cancer, the actual rate of decrease is unknown. Studies have indicated that 30-54% of women in a screening population who test positive for HPV have been infected with multiple types; this circumstance makes it difficult to clearly attribute cervical cancer occurrences specifically to HPV types 16 and 18 (Massad, Einstein, Myers, et al., 2009). There is also the possibility that vaccination against only two types of HPV could allow other cancer-causing types of the virus to fill "the biological niche left behind after the elimination of HPV types 16 and 18" (Sawaya & Smith-McCune, 2007). These conditions make it possible that Gardasil might reduce the risk of cervical cancer by less than 70% (the percentage of cervical cancers currently believed to be caused by HPV types 16 and 18). Given this remaining risk from other types of HPV, some
health professionals felt that the vaccine could discourage some precautions (e.g., using condoms, abstinence) that could reduce the spread of other types of the virus, and it could also discourage women from receiving frequent Pap tests, leading to an increase in undetected cervical cancers that could subsequently occur (Haug, 2008).

The long-term efficacy of the vaccine had also not been studied in detail at the time of marketing approval. Data from Merck's original clinical trials only provided evidence of an antibody response for up to five years after vaccination. It was not known whether a booster shot might be needed for the HPV vaccination, although recent data suggests that booster shots are advisable for a number of other standard childhood vaccines (Luedtke, 2008).

The efficacy of the vaccine was primarily tested in female subjects between the ages of 16-26. Merck conducted serology bridging studies to examine the immune response of younger females in comparison with the response of the subjects in the efficacy trials. These studies indicated that the immune response of females 9-15 years old was non-inferior to that of females who were 16-23 years old (Merck, n.d.). However, direct efficacy data was not available for younger vaccine recipients; this lack of data troubled some critics, who felt that the testing of the vaccine on children at the lower end of the approved age range was too limited (Gostin & DeAngelis, 2007).

The newness of the vaccine also caused some hesitation about quickly adopting it as a required vaccine. Limited data were available about possible side effects that could emerge only after large-scale use, causing some critics to argue that it was premature to make it into a required vaccine (Judicial Watch, 2008). Long-term side effects of the vaccine and its long-term efficacy were not yet studied; and as noted, it was not yet known if booster shots would need to be given to maintain effectiveness (Merck, n.d.).
Cost and Delivery Issues

Gardasil has a complex dosing schedule, requiring three separate injections over a six month period; this schedule requires reliable follow-up for children receiving the vaccine. The vaccine is also costly: At $120 per dose for the patient, the base cost for each vaccinated child is about $360. On top of this cost, many physicians charge additional office visit fees (McCullough, 2007). These circumstances make Gardasil one of the most expensive vaccines. Initially, at least, insurance coverage for the vaccine was unclear and many physicians felt that it was inadequate, given the especially high cost of Gardasil.

Vaccines are generally distributed in a different manner from other drugs, which are distributed through pharmacies. Other than flu vaccines, which are commonly distributed through multiple outlets (workplaces, drugstores, etc.), most vaccines are stored and distributed directly by doctors. Some practices must invest as much as $50,000 in vaccine inventories, on top of refrigeration and supply management. They are also responsible for spoiled inventory and must insure the vaccines themselves (Johnson, 2007). The HPV vaccine would also add to the vaccination costs for families. The 12 generally recommended childhood vaccinations can add up to a total cost of $1250, and the addition of Gardasil could bring that price to around $1600 (Stobbe, 2006).

Discussion and Conclusions

A confluence of factors led to the reaction against the proposed HPV vaccination mandate. These factors become more apparent in a comparison with the introduction of the hepatitis B vaccine, which shares a number of attributes with the HPV vaccine. The virus that the hepatitis B vaccine protects against is also not spread through casual contact; it is most commonly contracted through sexual contact. The vaccine must be given to young children prior
to the initiation of sexual activity to be most effective, and the vaccine acts at least in part as a protection against cancer. Like Gardasil, the hepatitis B vaccine requires a course of three injections over six months.

Also like Gardasil, the primary hepatitis B vaccines are marketed by Merck. However, the hepatitis B vaccine mandates did not generate the amount of controversy and backlash that was encountered by Gardasil. The way in which hepatitis B vaccination became universal was different from the path pursued by Merck with Gardasil. The hepatitis B vaccine was first introduced in 1982, and the ACIP made an initial recommendation that only high-risk groups should be vaccinated. However, by the end of the 1980s it became apparent that high-risk groups were not being reached in substantial numbers, and the rates of hepatitis B infections and subsequent complications did not significantly decline (CDC, 2002). In 1991, the ACIP revisited its vaccination strategy; the committee noted that 4,000-5,000 people still died yearly from hepatitis B-related diseases, including liver cancer (CDC, 1991). Selective vaccination had been ineffective, in part because of the difficulty of reaching high-risk individuals, and since in many cases the source of infection for some people could not be located, so they could not be designated as vaccination targets. There were still about 1 million to 1.25 million people in the United States with chronic hepatitis B infections. Given these circumstances, the ACIP revised its recommendations and promoted a strategy that included making hepatitis B vaccination part of the standard infant vaccination schedule. (CDC, 1991)

This strategy to gain infant vaccination was largely implemented through the channels of public health professionals. The type of popular media campaign that Merck pursued during the approach to the introduction of Gardasil did not take place with the introduction of the hepatitis B vaccine. By 1993, a survey of family physicians and pediatricians indicated that most agreed
with the latest ACIP recommendations and had adopted them in their practice (Freed, Freeman, Clark, Konrad, & Pathman, 1996). In 1994, hepatitis B vaccinations for children were funded under the VFC program (Rothman & Rothman, 2009). By the late 1990s, most states and the District of Columbia had adopted some form of childhood hepatitis B vaccination mandate, and currently all states have one (Immunization Action Coalition, n.d.).

Despite the similarities between the vaccines, there were a number of circumstances that made the HPV vaccination mandate much more difficult to implement than the one for hepatitis B. The hepatitis B vaccine was administered to infants rather than adolescents, so the question of whether giving a vaccine to prevent a sexually transmitted disease would encourage reckless behavior was not an issue. The hepatitis B vaccine was given to both girls and boys, so gender issues were not involved. The cost issue was not as large: at about $72 for a full course of three shots rather than the $360 base price for Gardasil, the hepatitis B vaccine was substantially cheaper (CDC, n.d., *CDC Vaccine Price List*). Merck also did not run a direct-to-consumer advertising campaign for the hepatitis B vaccine, and whatever lobbying efforts it made on the vaccine's behalf were less apparent. Also, at the time when the hepatitis B vaccination mandates were implemented, Merck had maintained a much more positive public image, ranking among the "most admired" companies (Herskovits, 2007). However, in the aftermath of the Vioxx scandal, Merck's reputation had been severely damaged (Kolata, 2004). This circumstance allowed suspicion to arise about Merck's motives when it began aggressively marketing its expensive new vaccine.

The larger social and political context had also changed from 1982 to 2006. Public suspicion about the safety of vaccines had risen, especially following the scientifically discredited claim that there was a link between some vaccines and autism. The Vioxx
controversy and other cases of other drugs that had been withdrawn from the market (such as the anti-obesity combination drug Fen-Phen) raised awareness of the possibility that new drugs could have long-term side effects that might not show up for a number of years. The movement for "abstinence only" sex education had raised suspicions about any government actions, whether through sex education classes in public schools or a mandate for a vaccine against a sexually transmitted disease, which could conceivably motivate teenagers to engage in sexual activity.

There were thus multiple factors that led to the failure of the proposed HPV vaccination mandate for school girls. The circumstances that derailed the attempt to mandate HPV vaccinations suggest that new vaccines face an increasingly complex environment when they are introduced to the market.
Timeline

1842  Domenico Rigoni-Stern reported that cervical cancer was much less common among virgins and nuns than among women who had been married.

1976  Harald zur Hausen first suggests a link between HPV and cervical cancer.

1983  Harald zur Hausen publishes the results of a study that shows the presence of HPV in the cervical cancer tumors of most of the women under observation.

1998  Merck begins human testing of the potential HPV vaccine.

2002 – November  Merck announces positive efficacy results in Phase III clinical trial involving vaccination against HPV Type 16 virus.

2005 – April  Merck announces positive results for Phase III clinical trial of an improved version of its vaccine that targets HPV Types 6 and 11 (which cause approximately 90% of genital wart cases) and Types 16 and 18 (which cause approximately 70% of cervical cancer cases).

2006 – May 18  FDA’s Vaccines and Related Biological Products advisory panel meets to review Merck’s HPV vaccine, now called Gardasil. The panel supports the vaccine as safe and effective by five separate 13-0 votes.

2006 – June 8  The FDA announces marketing approval for Gardasil for use by females aged 9-26.

2006 – June 29  The CDC Advisory Committee on Immunization Practices recommends routine HPV vaccination for girls aged 11 and 12, with vaccination also permitted for girls 9 or older per their doctor's discretion.

2006 – September  Michigan becomes the first state to consider a bill making HPV vaccination mandated for sixth grade school girls.

2007 - January 23  A Virginia House of Delegates committee endorses a bill requiring girls entering the sixth grade to receive the HPV vaccine.

2007 – February 2  Texas Governor Rick Perry issues an executive order requiring girls entering the sixth grade to get the HPV vaccine.

2007- February 20  Merck announces that it will no longer lobby for mandated HPV vaccinations for school girls.
2007 - May  Bill blocking Governor Rick Perry's order for HPV vaccinations becomes law without his signature.

2008 – March  The CDC announces results of a study indicating that about 1 in 4 American teenage girls has a sexually transmitted disease, with HPV present in 18% of the girls in the study.

2008 - September  The FDA approves the marketing of Gardasil for prevention of cancer of the vagina and vulva caused by HPV.
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