
Assessing Mandatory HPV Vaccination: Who Should Call the Shots?

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I. Introduction

The human papillomavirus (HPV) is the most common sexually transmitted infection worldwide. In the United States, more than six million people are infected each year. Although most HPV infections are benign, two strains of HPV cause 70 percent of cervical cancer cases.¹ Two other strains of HPV are associated with 90 percent of genital warts cases.²

In June 2006, the Food and Drug Administration (FDA) approved the first vaccine against HPV. Sold as Gardasil, the quadrivalent vaccine is intended to prevent four strains of HPV associated with cervical cancer, precancerous genital lesions, and genital warts.³ Following FDA approval, the national Advisory Committee on Immunization Practices (ACIP) recommended routine vaccination for girls ages 11-12 with three doses of quadrivalent HPV vaccine.⁴ Thereafter, state legislatures around the country engaged in an intense effort to pass laws mandating vaccination of young girls against HPV. This activity was spurred in part by an intense lobbying campaign by Merck, the manufacturer of the vaccine.⁵

The United States has a robust state-based infrastructure for mandatory vaccination that has its roots in the 19th century. Mandating vaccination as a condition for school entry began in the early 1800s and is currently required by all 50 states for several common childhood infectious diseases.⁶ Some suggest that mandatory HPV vaccination for minor females fits squarely within this tradition.

Nonetheless, state efforts to mandate HPV vaccination in minors have raised a variety of concerns on legal, ethical, and social grounds. Unlike other diseases for which state legislatures have mandated vaccination for children, HPV is neither transmissible through casual contact nor potentially fatal during childhood. It also would be the first vaccine to be mandated for use exclusively in one gender. As such, HPV vaccine presents a new context for considering vaccine mandates.

In this paper, we review the scientific evidence supporting Gardasil's approval and the legislative actions in the states that followed. We then argue that mandatory HPV vaccination at this time is both unwarranted and unwise. While the emergence of an HPV vaccine reflects a potentially significant public health advance, the vaccine raises several concerns. First, the long-term safety and effectiveness of the vaccine are unclear, and serious adverse events reported shortly after the vaccine's approval raise questions about its short-term safety as well. In light of unanswered safety questions, the vaccine should be rolled out slowly, with risks carefully balanced against benefits in individual cases. Second, the legal and ethical justifications that have historically supported state-mandated vaccination do not support mandating HPV vaccine. Specifically, HPV does not threaten an imminent and significant risk to the health of oth-

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ers. Mandating HPV would therefore constitute an expansion of the state's authority to interfere with individual and parental autonomy. Engaging in such expansion in the absence of robust public discussion runs the risk of creating a public backlash that may undermine the goal of widespread HPV vaccine coverage and lead to public distrust of established childhood vaccine programs for other diseases. Third, the current sex-based HPV vaccination mandates present constitutional concerns because they require only girls to be vaccinated. Such concerns could lead to costly and protracted legal challenges. Finally, vaccination

types of HPV is the most important risk factor for cervical cancer precursors and invasive cervical cancer. Two strains in particular, 16 and 18, have been classified as carcinogenic to humans by the World Health Organization's international agency for research on cancer.¹¹ These strains account for 70 percent of cervical cancer cases¹² and are responsible for a large proportion of anal, vulvar, vaginal, penile, and urethral cancers.¹³

More than 200,000 women die of cervical cancer each year.¹⁴ The majority of these deaths take place in developing countries, which lack the screening programs and infrastructure for diagnosis, treatment, and prevention that exist in the United States. In the U.S., it is estimated that there were about 9,700 cases of invasive cervical cancer and about 3,700 deaths from cervical cancer in 2006, as compared with 500,000 cases and 288,000 deaths worldwide.¹⁵

Two other HPV types, 6 and 11, are associated with approximately 90 percent of anogenital warts. They are also associated with low grade cervical disease and recurrent respiratory papillomatosis (RRP), a disease consisting of recurrent warty growths in the larynx and respiratory tract. Juvenile onset RRP (JORRP), a rare disorder caused by exposure to HPV during the peripartum period, can cause significant airway obstruction or lead to squamous cell carcinoma with poor prognosis.¹⁶

Although HPV types 6, 11, 16, and 18 are associated with significant morbidity and mortality, they have a fairly low prevalence in the U.S. population. One study of sexually active women ages 18 to 25 found HPV 16 and 18 prevalence to be 7.8 percent.¹⁷ Another study found overall prevalence of types 6, 11, 16, and 18 to be 1.3 percent, 0.1 percent, 1.5 percent, and 0.8 percent, respectively.¹⁸

B. Gardasil Safety and Effectiveness

Gardasil was approved based on four randomized, double blind, placebo-controlled studies in 21,000 women ages 16 to 26. Girls as young as nine were included in the safety and immunogenicity studies but not the efficacy studies. The results demonstrated that in women without prior HPV infection, Gardasil was nearly 100 percent effective in preventing precancerous cervical lesions, precancerous vaginal and vulvar lesions, and genital warts caused by vaccine-type HPV. Although the study period was not long enough for cervical cancer to develop, the prevention of these cervical precancerous lesions was considered a valid surrogate marker for cancer prevention. The studies

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mandates will place economic burdens on federal and state governments and individual practitioners that may have a negative impact on the provision of other health services. In light of these potentially adverse public health, economic, and societal consequences, we believe that it is premature for states to add HPV to the list of state-mandated vaccines.

II. Background

Before discussing in detail the basis for our opposition to mandated HPV vaccination, it is necessary to review the public health impact of HPV and the data based on which the FDA approved the vaccine. Additionally, to understand the potentially widespread uptake of HPV vaccine mandates, we review the state legislative activities that have occurred since the vaccine's approval.

A. HPV Epidemiology

In the United States, an estimated 20 million people, or 15 percent of the population, are currently infected with HPV.⁷ Modeling studies suggest that up to 80 percent of sexually active women will have become infected with the virus at some point in their lives by the time they reach age 50.⁸ Prevalence of HPV is highest among sexually active females ages 14-19.⁹

Human papillomavirus comprises more than 100 different strains of virus, of which more than 30 infect the genital area.¹⁰ The majority of HPV infections are transient, asymptomatic, and cause no clinical problems. However, persistent infection with high risk

also show that the vaccine is only effective when given prior to infection with high-risk strains.¹⁹

Gardasil is the second virus-like particle (VLP) vaccine to be approved by the FDA; the first was the Hepatitis B vaccine. VLPs consist of viral protein particles derived from the structural proteins of a virus. These particles are nearly identical to the virus from which they were derived but lack the virus's genetic material required for replication, so they are noninfectious and nononcogenic. VLPs offer advantages over more traditional peptide vaccines as the human body is more highly attuned to particulate antigens, which leads to a stronger immune response since VLP vaccines cannot revert to an infectious form, such as attenuated particles or incompletely killed particles.

No serious Gardasil-related adverse events were observed during clinical trials. The most common adverse event reported were injection site reactions, including pain, redness, and swelling.²⁰ The most common systemic adverse reactions experienced at the same rate by both vaccine and placebo recipients were headache, fever, and nausea. Five vaccine recipients reported adverse vaccine-related experiences: bronchospasm, gastroenteritis, headache with hypertension, joint movement impairment near injection site, and vaginal hemorrhage. Women with positive pregnancy tests were excluded from the studies, as were some women who became pregnant following receipt of either vaccine or placebo. The incidence of spontaneous pregnancy loss and congenital anomalies were similar in both groups.²¹ Gardasil was assigned pregnancy risk category B by the FDA on the basis that animal reproduction studies failed to demonstrate a risk to the fetus.²²

As of June 2007, the most recent date for which CDC has made data available, there were 1,763 reports of potential side effects following HPV vaccination made to the CDC's Vaccine Adverse Event Reporting System (VAERS). Ninety-four of these were defined as serious, including 13 unconfirmed reports of Guillain-Barre syndrome (GBS), a neurological illness resulting in muscle weakness and sometimes in paralysis. The CDC is investigating these cases. Seven deaths were also reported among females who received the vaccine, but the CDC stated that none of these deaths appeared to be caused by vaccination.²³

Although the FDA approved the vaccine for females ages 9-26, based on the data collected in those age groups, the ACIP recommendation for vaccination is limited to females ages 11-12. This recommendation was based on several considerations, including age of sexual debut in the United States and the high probability of HPV acquisition within several years of sexual debut, cost-effectiveness evaluations, and the

established young adolescent health care visit at ages 11-12 when other vaccines are also recommended.

C. State Legislative Activities

Since the approval of Gardasil, legislators in 41 states and the District of Columbia have introduced legislation addressing the HPV vaccine.²⁴ Legislative responses to Gardasil have focused on the following recommendations: (1) mandating HPV vaccination of minor girls as a condition for school entrance; (2) mandating insurance coverage for HPV vaccination or providing state funding to defray or eliminate cost of vaccination; (3) educating the public about the HPV vaccine; and/or (4) establishing committees to make recommendations about the vaccine.

In 2007, 24 states and the District of Columbia introduced legislation specifically to mandate the HPV vaccine as a condition for school entry.²⁵ Of these, only Virginia and Washington, D.C. passed laws requiring HPV vaccination. The Virginia law requires females to receive three properly spaced doses of HPV vaccine, with the first dose to be administered before the child enters sixth grade. A parent or guardian may refuse vaccination for his child after reviewing "materials describing the link between the human papillomavirus and cervical cancer approved for such use by the Board of Health."²⁶ The law will take effect October 1, 2008.

Additionally, the D.C. City Council passed the HPV Vaccination and Reporting Act of 2007, which directs the mayor to establish an HPV vaccination program "consistent with the standards set forth by the Centers for Disease Control for all females under the age of 13 who are residents of the District of Columbia."²⁷ The program includes a "requirement that the parent or legal guardian of a female child enrolling in grade 6 for the first time submit certification that the child has received the HPV vaccine" and a provision that "allows a parent or guardian to opt out of the HPV vaccination requirement." It also directs the mayor to develop reporting requirements "for the collection and analysis [*sic*] of HPV vaccination data within the District of Columbia Department of Health," including "annual reporting to the Department of Health as to the immunization status of each female child entering grade 6." The law requires Congressional approval in order to take effect.

In contrast, an Executive Order issued by the Texas governor was thwarted by that state's legislature. Executive Order 4, signed by Governor Rick Perry on February 4, 2007, would have directed the state's health department to adopt rules mandating the "age appropriate vaccination of all female children for HPV prior to admission to the sixth grade."²⁸ It would have

allowed parents to “submit a request for a conscientious objection affidavit form via the Internet.” However, H.B. 1098, enacted by the Texas state legislature on April 26, 2007, states that HPV immunization is “not required for a person’s admission to any elementary or secondary school,” and “preempts any contrary order issued by the governor.”²⁹ The bill was filed without the governor’s signature and became effective on May 8, 2007.

Of the 22 other states in which legislation mandating HPV vaccination was introduced in 2007, all would have required girls to be vaccinated somewhere between ages 11 and 13 or before entry into sixth grade. Most would have provided for some sort of parental or guardian exemption, whether for religious, moral, medical, cost, or other reasons. However, vaccine mandate bills in California and Maryland were withdrawn.

Bills requiring insurance companies to cover HPV vaccination or allocating state funds for this purpose were enacted in eight states.³⁰ Eight states also enacted laws aimed at promoting awareness of the HPV vaccine using various mechanisms, such as school-based distribution of educational materials to parents of early adolescent children.³¹ Finally, three states established expert bodies to engage in further study of HPV vaccination either instead of or as an adjunct to other educational efforts.³²

In total, 41 states and D.C. introduced legislation addressing HPV vaccination in some manner during the 2007 legislative session, and 17 of these states enacted laws relating to HPV vaccination.

III. Why Mandating HPV is Premature

The approval of a vaccine against cancer-causing HPV strains is a significant public health advance. Particularly in developing countries, which lack the health care resources for routine cervical cancer screening, preventing HPV infection has the potential to save millions of lives. In the face of such a dramatic advance, opposing government-mandated HPV vaccination may seem foolhardy, if not heretical. Yet strong legal, ethical, and policy arguments underlie our position that state-mandated HPV vaccination of minor females is premature.

A. Long-Term Safety and Effectiveness of the Vaccine is Unknown

Although the aim of clinical trials is to generate safety and effectiveness data that can be extrapolated to the general population, it is widely understood that such

trials cannot reveal all possible adverse events related to a product. For this reason, post-market adverse event reporting is required for all manufacturers of FDA-approved products, and post-market surveillance (also called “phase IV studies”) may be required in certain circumstances. There have been numerous examples in recent years in which unforeseen adverse reactions following product approval led manufacturers to withdraw their product from the market. For example, in August 1998, the FDA approved Rotashield, the first

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vaccine for the prevention of rotavirus gastroenteritis in infants. About 7,000 children received the vaccine before the FDA granted the manufacturer a license to market the vaccine. Though a few cases of intussusception, or bowel obstruction, were noted during clinical trials, there was no statistical difference between the overall occurrence of intussusception in vaccine compared with placebo recipients. After administration of approximately 1.5 million doses of vaccine, however, 15 cases of intussusception were reported, and were found to be causally related to the vaccine. The manufacturer subsequently withdrew the vaccine from the market in October 1999.³³

In the case of HPV vaccine, short-term clinical trials in thousands of young women did not reveal serious adverse effects. However, the adverse events reported since the vaccine’s approval are, at the very least, a sobering reminder that rare adverse events may surface as the vaccine is administered to millions of girls and young women. Concerns have also been raised that other carcinogenic HPV types not contained in the vaccines will replace HPV types 16 and 18 in the pathological niche.

The duration of HPV vaccine-induced immunity is unclear. The average follow-up period for Gardasil during clinical trials was 15 months after the third dose of the vaccine. Determining long-term efficacy is complicated by the fact that even during naturally occurring HPV infection, HPV antibodies are not detected in many women. Thus, long-term, follow-up post-licensure studies cannot rely solely upon sero-

logic measurement of HPV-induced antibody titers. One study indicates that protection against persistent HPV 16 infection remained at 94 percent 3.5 years after vaccination with HPV 16.³⁴ A second study showed similar protection for types 16 and 18 after 4.5 years.³⁵

The current ACIP recommendation is based on assumptions about duration of immunity and age of sexual debut, among other factors. As the vaccine is used for a longer time period, it may turn out that a different vaccine schedule is more effective. In addition, the effect on co-administration of other vaccines with regard to safety is unknown, as is the vaccines' efficacy with varying dose intervals. Some have also raised concerns about a negative impact of vaccination on cervical cancer screening programs, which are highly effective at reducing cervical cancer mortality. These unknowns must be studied as the vaccine is introduced in the broader population.

At present, therefore, questions remain about the vaccine's safety and the duration of its immunity, which call into question the wisdom of mandated vaccination. Girls receiving the vaccine face some risk of potential adverse events as well as risk that the vaccine will not be completely protective. These risks must be weighed against the state's interest in protecting the public from the harms associated with HPV. As discussed in the next section, the state's interest in protecting the public health does not support mandating HPV vaccination.

B. Historical Justifications for Mandated Vaccination are Not Met

HPV is different in several respects from the vaccines that first led to state-mandated vaccination. Compulsory vaccination laws originated in the early 1800s and were driven by fears of the centuries-old scourge of smallpox and the advent of the vaccine developed by Edward Jenner in 1796. By the 1900s, the vast majority of states had enacted compulsory smallpox vaccination laws.³⁶ While such laws were not initially tied to school attendance, the coincidental rise of smallpox outbreaks, growth in the number of public schools, and compulsory school attendance laws provided a rationale for compulsory vaccination to prevent the spread of smallpox among school children as well as a means to enforce the requirement by barring unvaccinated children from school.³⁷ In 1827, Boston became the first city to require all children entering public school to provide evidence of vaccination.³⁸ Similar laws were enacted by several states during the latter half of the 19th century.³⁹

The theory of herd immunity, in which the protective effect of vaccines extends beyond the vaccinated

individual to others in the population, is the driving force behind mass immunization programs. Herd immunity theory proposes that, in diseases passed from person to person, it is difficult to maintain a chain of infection when large numbers of a population are immune. With the increase in number of immune individuals present in a population, the lower the likelihood that a susceptible person will come into contact with an infected individual. There is no threshold value above which herd immunity exists, but as vaccination rates increase, indirect protection also increases until the infection is eliminated.

Courts were soon called on to adjudicate the constitutionality of mandatory vaccination programs. In 1905, the Supreme Court decided the seminal case, *Jacobson v. Massachusetts*,⁴⁰ in which it upheld a population-wide smallpox vaccination ordinance challenged by an adult male who refused the vaccine and was fined five dollars. He argued that a compulsory vaccination law was "hostile to the inherent right of every freeman to care for his own body and health in such way as to him seems best." The Court disagreed, adopting a narrower view of individual liberty and emphasizing the duties that citizens have towards each other and to society as a whole. According to the Court, the "liberty secured by the Constitution of the United States...does not import an absolute right in each person to be, at all times and in all circumstances, wholly freed from restraint. There are manifold restraints to which every person is necessarily subject for the common good." With respect to compulsory vaccination, the Court stated that "[u]pon the principle of self-defense, of paramount necessity, a community has the right to protect itself against an epidemic of disease which threatens the safety of its members." In the Court's opinion, compulsory vaccination was consistent with a state's traditional police powers, i.e., its power to regulate matters affecting the health, safety, and general welfare of the public.

In reaching its decision, the Court was influenced both by the significant harm posed by smallpox — using the words "epidemic" and "danger" repeatedly — as well as the available scientific evidence demonstrating the efficacy of the vaccine. However, the Court also emphasized that its ruling was applicable only to the case before it, and articulated principles that must be adhered to for such an exercise of police powers to be constitutional. First, there must be a public health necessity. Second, there must be a reasonable relationship between the intervention and public health objective. Third, the intervention may not be arbitrary or oppressive. Finally, the intervention should not pose a health risk to its subject. Thus, while *Jacobson* "stands firmly for the proposition that

police powers authorize states to compel vaccination for the public good,” it also indicates that “government power must be exercised reasonably to pass constitutional scrutiny.”⁴¹ In the 1922 case *Zucht v. King*,⁴² the Court reaffirmed its ruling in *Jacobson* in the context of a school-based smallpox vaccination mandate.

The smallpox laws of the 19th century, which were almost without exception upheld by the courts, helped lay the foundation for modern immunization statutes. Many modern-era laws were enacted in response to the transmission of measles in schools in the 1960s and 1970s. In 1977, the federal government launched the Childhood Immunization Initiative, which stressed the importance of strict enforcement of school immunization laws.⁴³ Currently, all states mandate vaccination as a condition for school entry, and in deciding whether to mandate vaccines, are

ACIP recommended vaccines. School-aged children are most at risk while in school because they are more likely to be in close proximity to each other in that setting. All children who attend school are equally at risk of both transmitting and contracting the diseases. Thus, a clear relationship exists between conditioning school attendance on vaccination and the avoidance of the spread of infectious disease within the school environment. Tetanus, a non-contagious disease, is somewhat different, but school-based vaccination can nevertheless be justified in that children will foreseeably be exposed within the school environment (e.g., on the playground) and, if exposed, face a high risk of mortality.

HPV vaccination, in contrast, does not satisfy these two principles. HPV infection presents no public health necessity, as that term was used in the context of *Jacobson*. While non-sexual transmission routes are theoretically possible, they have not been demonstrated. Like other sexually transmitted diseases which primarily affect adults, it is not immediately life threatening; as such, cervical cancer, if developed, will not manifest for years if not decades. Many women will never be exposed to the cancer-causing strains of HPV; indeed the prevalence of these strains in the U.S. is quite low. Furthermore, many who are exposed will not go on to develop cervical cancer. Thus, conditioning school attendance on HPV vaccination serves only to coerce compliance in the absence of a public health emergency.⁴⁵

The relationship between the government’s objective of preventing cervical cancer in women and the means used to achieve it — that is, vaccination of all girls as a condition of school attendance — lacks sufficient rationality. First, given that HPV is transmitted through sexual activity, exposure to HPV is not directly related to school attendance.⁴⁶ Second, not all children who attend school are at equal risk of exposure to or transmission of the virus. Those who abstain from sexual conduct are not at risk for transmitting or contracting HPV. Moreover, because HPV screening tests are available, the risk to those who choose to engage in sexual activity is significantly minimized. Because it is questionable how many school-aged children are actually at risk — and for those who are at risk, the risk is not linked to school attendance — there is not a sufficiently rational reason to tie mandatory vaccination to school attendance.

To be sure, the public health objective that proponents of mandatory HPV vaccination seek to achieve is compelling. Vaccinating girls before sexual debut

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guided by ACIP recommendations. At present, ACIP recommends vaccination for diphtheria, tetanus, and acellular pertussis (DTaP), Hepatitis B, polio, measles, mumps, and rubella (MMR), varicella (chicken pox), influenza, rotavirus, haemophilus Influenza B (HiB), pneumococcus, Hepatitis A, meningococcus, and, most recently HPV. State mandates differ; for example, whereas all states require DTaP, polio, and measles in order to enter kindergarten, most do not require Hepatitis A.⁴⁴

HPV is different from the vaccines that have previously been mandated by the states. With the exception of tetanus, all of these vaccines fit comfortably within the “public health necessity” principle articulated in *Jacobson* in that the diseases they prevent are highly contagious and are associated with significant morbidity and mortality occurring shortly after exposure. And, while tetanus is not contagious, exposure to *Clostridium tetani* is both virtually unavoidable (particularly by children, given their propensity to both play in the dirt and get scratches), life threatening, and fully preventable only through vaccination. Thus, the public health necessity argument plausibly extends to tetanus, albeit for different reasons.

Jacobson’s “reasonable relationship” principle is also clearly met by vaccine mandates for the other

provides an opportunity to provide protection against an adult onset disease. This opportunity is lost once sexual activity begins and exposure to HPV occurs. However, that HPV vaccination may be both medically justified and a prudent public health measure is an insufficient basis for the state to compel children to receive the vaccine as a condition of school attendance.

C. In the Absence of Historical Justification, the Government Risks Public Backlash by Mandating HPV Vaccination

Childhood vaccination rates in the United States are very high; more than half of the states report meeting the Department of Health and Human Services (HHS) Healthy People 2010 initiative's goal of ≥ 95 percent vaccination coverage for childhood vaccination.⁴⁷ However, from its inception, state mandated vaccination has been accompanied by a small but vocal anti-vaccination movement. Opposition has historically been "fueled by general distrust of government, a rugged sense of individualism, and concerns about the efficacy and safety of vaccines."⁴⁸ In recent years, vaccination programs also have been a "victim of their tremendous success,"⁴⁹ as dreaded diseases such as measles and polio have largely disappeared in the United States, taking with them the fear that motivated past generations. Some have noted with alarm the rise in the number of parents opting out of vaccination and of resurgence in anti-vaccination rhetoric making scientifically unsupported allegations that vaccination causes adverse events such as autism.⁵⁰

The rash of state legislation to mandate HPV has led to significant public concern that the government is overreaching its police powers authority. As one conservative columnist has written, "[F]or the government to mandate the expensive vaccine for children would be for Big Brother to reach past the parents and into the home."⁵¹ While some dismiss sentiments such as this one as simply motivated by right wing moral politics, trivializing these concerns is both inappropriate and unwise as a policy matter. Because sexual behavior is involved in transmission, not all children are equally at risk. Thus, it is a reasonable exercise of a parent's judgment to consider his or her child's specific risk and weigh that against the risk of vaccination.

To remove parental autonomy in this case is not warranted and also risks parental rejection of the vaccine because it is perceived as coercive. In contrast, educating the public about the value of the vaccine may be highly effective without risking public backlash. According to one poll, 61 percent of parents with daughters under 18 prefer vaccination, 72 percent would support the inclusion of information about

the vaccine in school health classes, and just 45 percent agreed that the vaccine should be included as part of the vaccination routine for all children and adolescents.⁵²

Additionally, Merck's aggressive role in lobbying for the passage of state laws mandating HPV has led to some skepticism about whether profit rather than public health has driven the push for state mandates.⁵³ Even one proponent of state-mandated HPV vaccination acknowledges that Merck "overplayed its hand" by pushing hard for legislation mandating the vaccine.⁵⁴ In the face of such criticisms, the company thus ceased its lobbying efforts but indicated it would continue to educate health officials and legislators about the vaccine.⁵⁵

Some argue that liberal opt-out provisions will take care of the coercion and distrust issues. Whether this is true will depend in part on the reasons for which a parent may opt out and the ease of opting out. For example, a parent may not have a religious objection to vaccination in general, but nevertheless may not feel her 11-year-old daughter is at sufficient risk for HPV to warrant vaccination. This sentiment may or may not be captured in a "religious or philosophical" opt-out provision.

Even if opt-out provisions do reduce public distrust issues for HPV, however, liberal opt outs for one vaccine may have a negative impact on other vaccine programs. Currently, with the exception of those who opt out of all vaccines on religious or philosophical grounds, parents must accept all mandated vaccines because no vaccine-by-vaccine selection process exists, which leads to a high rate of vaccine coverage. Switching to an "a la carte" approach, in which parents can consider the risks and benefits of vaccines on a vaccine-by-vaccine basis, would set a dangerous precedent and may lead them to opt out of other vaccines, causing a rise in the transmission of these diseases. In contrast, an "opt in" approach to HPV vaccine would not require a change in the existing paradigm and would still likely lead to a high coverage rate.

D. Mandating HPV for Girls and Not Boys May Violate Constitutional Principles of Equality and Due Process

1. vaccination of males may protect them from hpv-related morbidity

The HPV vaccine is the first to be mandated for only one gender. This is likely because the vaccine was approved for girls and not boys. Data demonstrating the safety and immunogenicity of the vaccine are available for males aged 9-15 years. Three phase 1 studies demonstrated that safety, tolerance, and immunogenicity of the HPV vaccine were similar to men and

women. The first two studies focused on HPV 16 and 11, respectively, while the third study demonstrated high levels of immunogenicity to prophylactic HPV 6/11/16/18 vaccine in 10-15-year-old males.⁵⁶ Phase III clinical trials examining the vaccine's efficacy in men and adolescent boys are currently underway, with results available in the next couple of years.⁵⁷

HPV infection is common among men.⁵⁸ One percent of the male population aged 15-49 years has genital warts, with peak incidence in the 20-24-year-old age group.⁵⁹ A recent cohort study found the 24-month cumulative incidence of HPV infection among 240 men aged 18-20 years to be 62.4 percent, nearly double the incidence of their female counterparts.⁶⁰ This result may have been due to the increased sensitivity of the new HPV-PCR-based testing procedure used in the study. Nonetheless, the results reaffirm that HPV is common and multifocal in males. Males with genital warts have also been shown to carry the genital type specific HPV virus on their fingertips.⁶¹ While HPV on fingertips may be due to autoinoculation, it may also represent another means of transmission.⁶² Men are also at risk for HPV-related anogenital cancers. Up to 76 percent of penile cancers are HPV DNA positive.⁶³ Fifty-eight percent of anal cancers in heterosexual men and 100 percent among homosexual men are positive for HPV DNA.⁶⁴ Therefore, assuming vaccine efficacy is confirmed in males, they also could be protected through HPV vaccination.

2. INCLUDING MALES IN HPV VACCINATION MAY BETTER PROTECT THE PUBLIC THAN FEMALE VACCINATION ALONE

As no clinical trial data on vaccine efficacy in men has been published to date, mathematical models have been used to explore the potential benefits and cost effectiveness of vaccinating boys in addition to girls under various clinical scenarios. Even under the most generous assumption about vaccine efficacy in males and females, cost-effective analyses have found contradictory results. Several studies suggest that if vaccine coverage of women reaches 70-90 percent of the population, then vaccinating males would be of limited value and high cost.⁶⁵ Ruanne Barnabas and Geoffrey Garnett found that a multivalent HPV vaccine with 100 percent efficacy targeting males and females 15 years of age with vaccine coverage of at least 66 percent was needed to decrease cervical cancer by 80 percent. They concluded that vaccinating men in addition to women had little incremental benefit in

reducing cervical cancer,⁶⁶ that vaccine acceptability in males is unknown, and that in a setting with limited resources, the first priority in reducing cervical cancer mortality should be to vaccinate females.

Yet several models argue in favor of vaccinating males. Vaccination not only directly protects through vaccine-derived immunity, but also indirectly through herd immunity, meaning a level of population immunity that is sufficient to protect unvaccinated individuals. If naturally acquired immunity is low and cover-

Access to HPV is one reason that some proponents favor state mandates. They argue that in the absence of a state mandate, parents will not know to request the vaccine, or will not be able to afford it because it will not be covered by insurance companies or by federal or state programs that pay for vaccines for the uninsured and underinsured.

age of women is low, then vaccinating men will be of significant benefit. James Hughes et al. found that a female-only monovalent vaccine would be only 60-75 percent as efficient as a strategy that targets both genders.⁶⁷ Elamin Elbasha and Erik Dasbach found that while vaccinating 70 percent of females before the age of 12 would reduce genital warts by 83 percent and cervical cancer by 78 percent due to HPV 6/11/16/18, including men and boys in the program would further reduce the incidence of genital warts, CIN, and cervical cancer by 97 percent, 91 percent, and 91 percent, respectively.⁶⁸ In all mathematical models, lower female coverage made vaccination of men and adolescent boys more cost effective, as did a shortened duration of natural immunity.

All the models include parameters that are highly inferential and lacking in evidence, such as duration of vaccine protection, reactivation of infections, transmission of infection, and health utilities. The scope of the models is limited to cervical cancer, cancer-in-situ, and genital warts. None of the models accounts for HPV-related anal, head, and neck cancers, or recurrent respiratory papillomatosis. As more data become available, the scope of the models will be broadened and might strengthen the argument in favor of vaccinating males. Given that male vaccination may better protect the public than female vaccination alone, female-specific mandates may be constitutionally suspect, as discussed below.

3. the government must adequately justify its decision to mandate vaccination in females only

While courts have generally been deferential to state mandate laws, this deference has its limits. In 1900, a federal court struck a San Francisco Board of Health resolution requiring all Chinese residents to be vaccinated with a serum against bubonic plague about which there was little evidence of efficacy. Chinese residents were prohibited from leaving the area unless they were vaccinated. The court struck down the resolution as an unconstitutional violation of the Equal Protection and Due Process clauses. The court found that there was not a defensible scientific rationale for the board's approach and that it was discriminatory in targeting "the Asiatic or Mongolian race as a class." Thus, it was "not within the legitimate police power" of the government.⁶⁹

A sex-based mandate for HPV vaccination could

tected liberty interest in refusing unwanted medical treatment.⁷⁰ This liberty interest must, however, be balanced against several state interests, including its interest in preserving life. Mandated HPV laws interfere with the right of girls to refuse medical treatment, and therefore could be challenged under the Due Process Clause. Whether the government could demonstrate interests strong enough to outweigh a girl's liberty interest in refusing vaccination would depend on the strength of the government's argument that such vaccination is life-saving and the extent to which opt outs are available and easily exercised in practice.

Even if courts upheld government mandates as consistent with the Due Process and Equal Protection clauses, such mandates remain troubling in light of inequalities imposed by sex-based mandates and the liberty interests that would be compromised by HPV mandates, therefore placing deeply cherished national values at risk.

Based on the current scientific evidence, vaccinating girls against HPV before they are sexually active appears to provide significant protection against cervical cancer. The vaccine thus represents a significant public health advance. Nevertheless, mandating HPV vaccination at the present time would be premature and ill-advised.

be challenged on two grounds: first, under the Equal Protection Clause because it distinguishes based on gender and second, under the Due Process Clause, because it violates a protected interest in refusing medical treatment. In regard to the Equal Protection concerns, courts review laws that make sex-based distinctions with heightened scrutiny: the government must show that the challenged classification serves an important state interest and that the classification is at least substantially related to serving that interest. To be sure, courts would likely view the goal of preventing cervical cancer as an important public health objective. However, courts would also likely demand that the state justify its decision to burden females with the risks of vaccination, and not males, even though males also contribute to HPV transmission, will benefit from an aggressive vaccination program of females, and also may reduce their own risk of disease through vaccination.

With respect to the Due Process Clause, the Supreme Court has, in the context of right-to-die cases, recognized that individuals have a constitutionally pro-

E. Unresolved Economic Concerns

Mandated HPV vaccination may have negative unintended economic consequences for both state health departments and private physicians, and these consequences should be thoroughly considered before HPV vaccination is mandated. In recent years, state health departments have found themselves increasingly strapped by the rising number of mandated vaccines. Some states that once provided free vaccines to all

children have abandoned the practice due to rising costs. Adding HPV could drive more states to abandon funding for other vaccinations and could divert funding from other important public health measures. At the federal level, spending by the federal Vaccines for Children program, which pays for immunizations for Medicaid children and some others, has grown to \$2.5 billion, up from \$500 million in 2000.⁷¹ Such rapid increases in budgetary expenses affect the program's ability to assist future patients. Thus, before HPV vaccination is mandated, a thorough consideration of its economic consequences for existing vaccine programs and other non-vaccine programs should be undertaken.

The increasing number of vaccines has also placed a burden on physicians in private practice. Currently, about 85 percent of the nation's children get all or at least some of their inoculations from private physicians' offices.⁷² These offices must purchase vaccines and then wait for reimbursement from either government or private insurers. Some physicians have argued that the rising costs of vaccines and the rising

number of new mandatory vaccines make it increasingly difficult for them to purchase vaccinations initially and that they net a loss due to insufficient reimbursement from insurers. Adding HPV to the list of mandated vaccines would place further stress on these practices, and could lead them to reduce the amount of vaccines they purchase or require up-front payment for these vaccines. Either of these steps could reduce access not only to HPV but to all childhood vaccines.

Access to HPV is one reason that some proponents favor state mandates. They argue that in the absence of a state mandate, parents will not know to request the vaccine, or will not be able to afford it because it will not be covered by insurance companies or by federal or state programs that pay for vaccines for the uninsured and underinsured. However, mandates are not the only way to increase parental awareness or achieve insurance coverage. In light of the potentially significant economic consequences of state mandates, policymakers should consider other methods of increasing parental awareness and insurance coverage that do not also threaten to reduce access to those who want vaccination.

IV. Conclusion

Based on the current scientific evidence, vaccinating girls against HPV before they are sexually active appears to provide significant protection against cervical cancer. The vaccine thus represents a significant public health advance. Nevertheless, mandating HPV vaccination at the present time would be premature and ill-advised. The vaccine is relatively new, and long-term safety and effectiveness in the general population is unknown. Vaccination outcomes of those voluntarily vaccinated should be followed for several years before mandates are imposed. Additionally, the HPV vaccine does not represent a public health necessity of the type that has justified previous vaccine mandates. State mandates could therefore lead to a public backlash that will undermine both HPV vaccination efforts and existing vaccination programs. Finally, the economic consequences of mandating HPV are significant and could have a negative impact on financial support for other vaccines as well as other public health programs. These consequences should be considered before HPV is mandated.

The success of childhood vaccination programs makes them a tempting target for the addition of new vaccines that, while beneficial to public health, exceed the original justifications for the development of such programs and impose new financial burdens on both the government, private physicians, and, ultimately, the public. HPV will not be the last disease that state legislatures will attempt to prevent through manda-

tory vaccination. Thus, legislatures and public health advocates should consider carefully the consequences of altering the current paradigm for mandatory childhood vaccination and should not mandate HPV vaccination in the absence of a new paradigm to justify such an expansion.

Note

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