

Mandatory HPV Vaccination

Public Health vs Private Wealth

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BY ANY MEASURE, GENITAL HUMAN PAPILLOMAVIRUS (HPV) infection and HPV-associated cervical cancer are significant national and global public health concerns. An estimated 11 000 newly diagnosed cases of cervical cancer occur annually in the United States, resulting in 3700 deaths.¹ Globally, an estimated 493 000 new cervical cancer cases occur each year, with 274 000 deaths; more than 80% of cervical cancer deaths worldwide occur in developing countries.²

Human papillomavirus is the most common sexually transmitted infection in the United States, with an estimated 6.2 million individuals newly infected annually.³ Data from the National Health and Nutrition Examination Survey revealed a 26.8% overall HPV prevalence among US girls and women, with increasing prevalence each year for ages 14 to 24 years (44.8% for ages 20-24 years) followed by a gradual decline in prevalence through age 59 years (19.6% for ages 50-59 years).⁴ Although infection with high-risk HPV types is necessary for the development of cervical cancer (detected in 99% of cervical cancers),⁵ high-risk types 16 and 18 have a relatively low prevalence (3.4% of all HPV infections),⁴ and not all women who are infected with high-risk HPV types will develop cervical cancer. Approximately 90% of women with new HPV infections clear the infection within 2 years.⁶

In June 2006, the US Food and Drug Administration (FDA) licensed a prophylactic quadrivalent HPV vaccine against types 6, 11, 16, and 18 for use among girls and women aged 9 to 26 years.⁷ The FDA approval is conditional on manufacturer assurances concerning ongoing safety and efficacy studies.⁸ The Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination of girls aged 11 to 12 years with 3 doses of quadrivalent HPV vaccine; the vaccination series can be started as young as age 9 years.⁹ ACIP also recommends "catch-up" vaccination for unvaccinated girls and women aged 13 to 26 years.⁹

Clinical trials among 16- to 26-year-olds show that the quadrivalent HPV vaccine is almost 100% effective in preventing infection and disease associated with HPV types included in the vaccine.¹⁰ Studies show that the vaccine is safe

and immunogenic for girls aged 9 to 15 years for at least a short term, but efficacy among this age group has not been evaluated. For those older than 15 years, the vaccine provides protection for at least 5 years, and follow-up studies are under way to determine the duration of protection.⁹ A bivalent vaccine against HPV types 16 and 18 also has been shown to be highly immunogenic and safe for up to 4.5 years, although it is not yet licensed.¹¹

Earlier this year, Texas (by executive order) and Virginia made quadrivalent HPV vaccine mandatory for girls entering sixth grade. However, the Texas legislature recently voted to overturn the governor's order and Virginia granted parents generous "opt-out" provisions.¹² Nearly 20 additional states are considering similar legislation,¹³ and some medical experts in Europe are calling for mandatory HPV vaccination.¹⁴ Routine use of the quadrivalent HPV vaccine undoubtedly is beneficial to the public's health, as it is likely to reduce the incidence of cervical cancers. However, the rush to make HPV vaccination mandatory in school-aged girls presents ethical concerns and is likely to be counterproductive.

The ACIP recommendation supports making quadrivalent vaccination the standard of clinical care. However, it is important to emphasize that the vaccine is supported by limited efficacy and safety data. Clinical trials have thus far involved a relatively small population (<12 000 participants) for a limited period of follow-up (5 years). The vaccine has not been evaluated for efficacy among younger girls (aged 9 to 15 years). Yet, if the vaccine were required nationwide, it would be administered to some 2 million girls and young women, most of them between 11 and 12 years old and some as young as 9 years old. The longer-term effectiveness and safety of the vaccine still need to be evaluated among a large population, and particularly among younger girls.

Given that the overall prevalence of HPV types associated with cervical cancer is relatively low (3.4%)⁴ and that the long-term effects are unknown, it is unwise to require a young girl with a very low lifetime risk of cervical cancer to be vaccinated without her assent and her parent's consent. Consider the information a clinician can honestly provide

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to a 12-year-old girl to obtain her assent: "The 3 injections will probably protect you from an infection that you can only get from sexual contact, but research has not shown how long the protection will last or whether it might have bad effects on your health." Although many clinicians who have spent most of their professional lives caring for children and adolescents might recommend the vaccine, they would be troubled if the patient and her family felt pressured or coerced.

Making the HPV vaccine mandatory contributes to longstanding parental concerns about the safety of school-based vaccinations.¹⁵ The use of compulsion, therefore, could have the unintended consequence of heightening parental and public apprehensions about childhood vaccinations. It also does not help to offer generous religious and conscientious exemptions for HPV vaccination because legislators may extend these to other childhood vaccinations, which would be detrimental to the public's health.¹⁶

Another important consideration is how vaccine recipients would be compensated if they incurred serious adverse effects in the future as a result of a vaccine that the state required. By making the vaccine mandatory, the state would probably complicate tort claims, with some courts holding that the manufacturer had no (or reduced) responsibility for consumer harms. Ethically, if the state mandates an intervention, it should also provide a compensation system, for example, through the no-fault National Vaccine Injury Compensation Program. As with other vaccines, issues of legal liability and fair compensation must be considered carefully.

Public health authorities, pediatricians, and infectious disease specialists, rather than political bodies, should drive mandatory vaccination decisions and policies. The Centers for Disease Control and Prevention recommend routine use of HPV vaccinations, but that is not equivalent to mandatory use. Merck, the manufacturer of the HPV quadrivalent vaccine, lobbied legislatures to make the vaccine mandatory¹⁷ before withdrawing its campaign when it became controversial.¹⁸ Since the manufacturer stands to profit from widespread vaccine administration, it is inappropriate for the company to finance efforts to persuade states and public officials to make HPV vaccinations mandatory, particularly so soon after the product was licensed. Private wealth should never trump public health.

Human papillomavirus is not a highly infectious airborne disease, which is the paradigm for the exercise of compulsory vaccination. There is no immediate risk of rapid transmission of HPV in schools, as is the case, for example, with measles. The HPV vaccine does not create herd immunity, although it would probably reduce the prevalence of HPV infections. The primary justification for HPV vaccination is to protect women from long-term risks, rather than to prevent immediate harm to others. This may not be a definitive argument against universal use of HPV vaccine because states already mandate vaccination against an-

other disease (hepatitis B) that can be transmitted sexually (among other routes of exposure). But because the HPV vaccine is not immediately necessary to prevent harm to others, it does suggest that compulsory measures need to be more carefully thought through.

The ACIP probably recommended routine vaccination for girls only because the data are limited to that sex. However, if compulsory powers were justified on classic public health grounds, the same arguments could and should apply to vaccination of boys. While less is known about HPV prevalence in men, some studies have shown that men can have at least as high a prevalence of HPV infection as women,¹⁹ and they are just as likely to transmit the infection to their partners. 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.

There is also the question of cost—who will pay for the mandated HPV vaccine and what other public health services would society have to forgo because of the cost? The estimated cost of quadrivalent HPV vaccine is \$360 for a 3-course series, making it among the most expensive of all vaccines.¹⁷ Cost-effectiveness studies of HPV vaccination have had variable results, depending on assumptions about effectiveness and safety.²⁰ Some pediatricians and other physicians are not offering the most costly vaccines because they cannot afford to purchase them, and they cannot be certain about full reimbursement.^{21,22} Policy makers also have not answered the question of who will pay: consumers, insurers, or federal, state, or local government (ie, taxpayers). If consumers or insurers were to pay, poor and uninsured persons would be unable to afford the vaccine, which would exacerbate health disparities. If the government were to pay, it would have to find the funds from its general revenues, perhaps reducing public health spending for other programs.

Years from now, when additional data and experience better inform clinicians and policy makers about the risks and benefits, states might consider requiring HPV vaccination as a condition of school entry. But for now, it is preferable to take a deliberative approach and view routine, voluntary HPV vaccination as part of a comprehensive package for preventing sexually transmitted infections and cervical cancer. A systematic approach to prevention would include promoting reduced sexual activity and safer forms of sex, cervical cancer screening (eg, Papanicolaou tests and HPV testing), and education about HPV and cervical cancer among schoolchildren, health care professionals, and the general public. Interventions are particularly important among African American and Hispanic women, who have disproportionate burdens of cervical cancer.²³

These important concerns about mandatory HPV vaccination are not motivated by morals, as there are no data to suggest that an appropriately conducted public health program encourages sexual activity. Rather, maintaining the public's trust is vital—both for HPV vaccination in particular

and for school-based vaccination programs more generally.²⁴ Legislation to make HPV vaccine mandatory has undermined public confidence and created a backlash among parents. There is nothing more important to the success of public health policies than to ensure community acceptability. In the absence of an immediate risk of serious harm, it is preferable to adopt voluntary measures, making state compulsion a last resort.²⁵

Financial Disclosures: None reported.

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Translating MicroRNA Discovery Into Clinical Biomarkers in Cancer

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IN THE UNITED STATES, CANCER IS THE SECOND LEADING cause of death, exceeded only by cardiovascular disease, and an estimated 500 000 patients with cancer will die this year.^{1,2} After cardiovascular and infectious diseases, cancer is the third leading cause of mortality worldwide.³ However, the field of clinical oncology is poised for unprecedented innovation, reflecting the confluence of breakthroughs in decoding disease pathobiology in the context of high-throughput enabling technologies.⁴ Harnessing the full potential of transformative advances is predicated on defining biomarkers that promote targeted cancer prevention, diagnosis, and treatment of individual patients and populations.^{4,5} A new generation of molecular technolo-

gies, including genomic, proteomic, and metabolomic mapping, hold the promise of translating into practice the use of biomarker panels for increased diagnostic and therapeutic sensitivity and specificity.^{2,4} Yet essential elements have resisted definition in developing mechanism-based molecular markers for individualized management of cancer. In particular, the hierarchically organized integrated epigenetic, genetic, and postgenetic circuitry that dictates developmental restriction of cell destiny and underlies tumorigenesis when dysregulated has so far remained poorly understood.

Emerging science has revealed a layer of genetic programmatic coordination by which cells determine their fate; this layer involves posttranscriptional regulation of gene expres-

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