

Human papillomavirus (HPV) vaccination: Where do we go from here?

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Human Papillomavirus

Human papillomavirus (HPV) is a family of over 100 related viruses that can affect many parts of the body. Approximately 30 types are known to infect the anogenital tract and are transmitted predominantly by sexual contact. Some types can lead to the development of cancer of the cervix, vulva, penis, and anus; these are called high-risk types. Those that can result in condylomas are rarely associated with cancer and are termed low-risk types [1,2].

Since HPV is not a reportable disease, there is no national surveillance data on the incidence of HPV. However, one recent nation-wide study found an HPV prevalence of 26.9% in women 18-25 years of age [3]. This is likely an underestimate as the study utilized urine samples, which have been shown in multiple comparison studies to under-report HPV prevalence by a factor of 1.2 to 1.3 compared to cervical samples [4-6]. Given this, it is not unreasonable to assume the actual prevalence in this group is closer to 33%. By the age of 50, over 80% of the female US population will have acquired a genital HPV infection at some point in their lives, making it the most common sexually transmitted infection (STI) [2].

Most infections with HPV will resolve spontaneously without resulting in any symptoms or significant adverse effects [1]. Infection with a high-risk type can lead to abnormal Pap smears, resulting in increased testing and possible treatment. Infection with low-risk types can lead to anogenital condylomas. These can be treated, though this is not curative, and some people will develop recurrences.

The most common serious potential long-term consequence of HPV infection is cervical cancer. According to the American Cancer Society, in 2006 an estimated 9,710 cases of invasive cervical cancer will be diagnosed and an estimated 3,700 women will die from cervical cancer. Death rates from cervical cancer have dropped dramatically in the United States, 74% from 1955 to 1992, largely due to the widespread use of the Pap test [7]. Worldwide, the numbers are much grimmer. In 2000 there were an estimated 470,600 new cases of cervical cancer, with 80% of those in developing countries. In addition, there were an estimated 233,400 deaths due to cervical cancer worldwide [8].

Nearly all cases of cervical cancer are associated with infection with a high-risk HPV type [9-11]. 90% of

infections with high-risk HPV types will become undetectable within 2 years of infection. Persistent infection with high-risk HPV types is the main risk factor for cervical cancer, putting the women with the remaining 10% of high-risk HPV infections at increased risk for cervical cancer [2].

Cost of HPV Infection

The medical costs associated with HPV in the United States are significant. Among 8 major STIs, HPV is second only to HIV in annual direct medical costs attributed to infection in individuals aged 15-24 with an estimated total of \$2.9 billion in 2000 (see Figure 1). 92.1% of costs associated with HPV are due to abnormal Pap smears and the treatment of cervical neoplasia; this is 4-fold greater than the combined costs for genital herpes, Chlamydia, Gonorrhea, Trichomoniasis, Hepatitis B, and Syphilis [12].

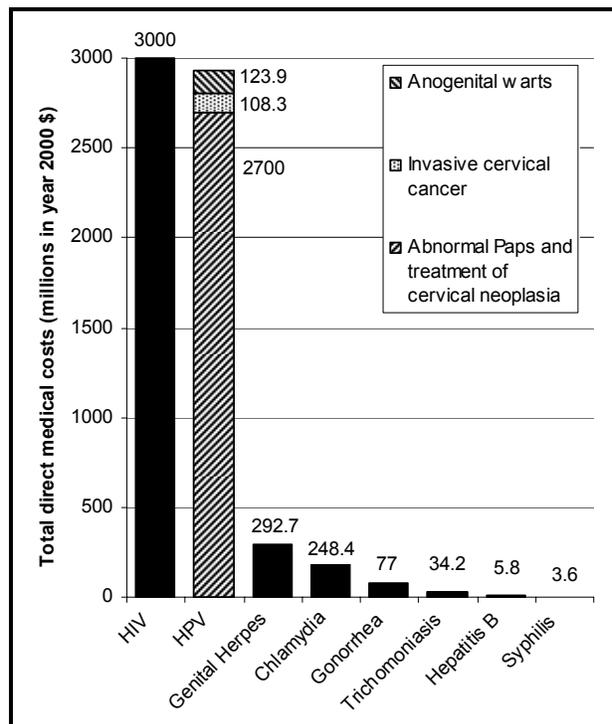


Figure 1. Estimated Total Direct Medical Costs due to 8 Major STIs in 15-24 year-old Americans in 2000.

Costs for HPV are broken into estimated direct costs for anogenital warts, invasive cervical cancer, and abnormal Pap results and treatment of cervical neoplasia. [12]

HPV Vaccines

With the successful development of a vaccine for hepatitis B virus (HBV) that protects against some forms of hepatocellular carcinoma, and given the strong association between cervical cancer and human papillomavirus, much research has been put into the development of a vaccine for HPV. Currently, the two companies that have shown the most promise with developing a vaccine for HPV are Merck and GlaxoSmithKline (GSK). Merck has developed a quadrivalent HPV vaccine, covering HPV types 6, 11, 16, and 18 [13]. The GSK vaccine covers HPV types 16 and 18 [14]. HPV types 16 and 18 are high-risk and are the two most common HPV types associated with cervical cancer, together accounting for 70% of all cervical cancer cases [11]. HPV types 6 and 11 are low-risk types associated with 90% of condyloma acuminatum [15,16]. Both vaccines utilize virus-like particles (VLPs) of the L1 capsid protein without the inclusion of any viral DNA, making transmission of the virus from the vaccine impossible [13,14].

The results of Phase II and III studies Merck's quadrivalent HPV vaccine (GARDASIL®) are very promising. In terms of safety, compared with a placebo consisting of an aluminum adjuvant, the vaccine was associated with an increased incidence of injection site pain (85.3% vs. 73.1%), erythema (26.8% vs. 19.4%), pruritis (2.9% vs. 0.7%), and swelling (27.9% vs. 13.9%). Systemic adverse reactions were generally comparable with the exception of dizziness (4.8% vs. 0.7%) and headache (40.4% vs. 35.8%). There were no serious adverse reactions that were determined to be vaccine-related [17]. While the study protocol did not allow for vaccination of pregnant women, there were cases of inadvertent administration of vaccine during pregnancy. 5 of 112 (4.5%) pregnancies that occurred in the vaccinated group with the estimated onset of pregnancy within 30 days of a vaccination resulted in a congenital anomaly, versus none in the control group. For pregnancies beyond 30 days of the estimated onset of pregnancy, the rate of congenital anomalies was 1.1% for the vaccinated group and 1.8% for the control group. Other measures of pregnancy, including live births, elective termination, and spontaneous loss, were similar between the two groups [18].

The efficacy of GARDASIL® in these studies is very impressive. One study, the FUTURE II study, enrolled 12,167 women from 13 countries, 6,082 subjects and 6,075 controls. In 17 months of follow-up after completion of the vaccination regimen in per-protocol test subjects, GARDASIL® was 100% effective in preventing HPV type 16 and 18 related cervical carcinoma *in situ* (AIS) and the high-grade precancerous cervical lesions: cervical intraepithelial neoplasia (CIN) grades 2 and 3 (95% confidence

interval 93%-100%). In addition, the vaccine was 100% effective in preventing HPV type 16 and 18 related high-grade pre-cancerous vulvar and vaginal lesions: vulvar intraepithelial neoplasia (VIN) grades 2 and 3 and vaginal intraepithelial neoplasia (VaIN) grades 2 and 3, respectively (95% confidence interval 55%-100%). In preventing CIN and AIS due to all four vaccinated HPV types (6, 11, 16, 18), GARDASIL® was 95% effective (95% confidence interval 87%-99%). Prevention of external genital lesions due to the four vaccinated HPV types was 99% efficacious (95% confidence interval 95%-100%). In a 5-year follow-up of per-protocol vaccine efficacy in 235 test subjects and 233 controls, there were only two cases of HPV infection in the test subjects versus 46 for the controls. One of the test subject HPV infections was with type 16 at the last visit of the follow-up without confirmed persistence of infection. The other was with type 18 at 12 and 18 months. Efficacies by HPV type (with 95% confidence interval) were: type 6 - 100% (76%-100%), type 11 - 100% (<0%-100%), type 16 - 97% (79%-100%), and type 18 - 91% (36%-100%) [18].

On June 8, 2006, the FDA approved Merck's recombinant vaccine GARDASIL® for the prevention of cervical cancer, condyloma acuminatum, cervical carcinoma *in situ* (AIS), CIN grade 1, and CIN, VIN, and VaIN grades 2 and 3 in females 9 to 26 years of age [19]. At the June 29, 2006, meeting of the Advisory Committee on Immunization Practices (ACIP), the committee recommended routine vaccination of 11-12 year-old females with GARDASIL®. In addition, they allowed the vaccination of females as young as 9 years at the discretion of the health care provider and of 13-26 year-old females. In their recommendation, the committee noted that those not yet sexually active and thus not yet exposed to HPV would receive the greatest benefit from the vaccine, but that those already sexually active should still receive the vaccine. These recommendations will become Center for Disease Control (CDC) policy once they are published in Morbidity and Mortality Weekly Report (MMWR) after approval by the director of the CDC and the Secretary of Health and Human Services [20]. At the same meeting, the ACIP added the quadrivalent HPV vaccine to the Vaccines for Children (VFC) Program [21].

Studies of the bivalent HPV vaccine for HPV types 16 and 18 from GSK, branded Cervarix®, have shown efficacy rates similar to GARDASIL® [14,22]. GSK has filed for international regulatory approval for Cervarix® with the European Agency for the Evaluation of Medicinal Products, in Australia, and in parts of Asia and Latin America. They plan to submit Cervarix® to the FDA by the end of 2006 [23].

Issues to Address

All indications suggest that a vaccine for human papillomavirus has the potential to substantially reduce the morbidity and mortality associated with HPV, both in the United States and worldwide. However, there are a number of issues to address in how to best utilize these new vaccines. Some are related to all vaccines while others are particular to this type of vaccine. Some of these issues will be addressed here.

Long-term protection

As with any vaccine, the duration of protection is an important consideration, not only in determining dosing interval recommendations but also in calculating cost effectiveness. With all new vaccines it is difficult if not impossible to predict the long-term efficacy. An estimate of long-term protection for HPV vaccines utilizing VLPs might be obtainable from looking at the HBV vaccine, which is also based on VLPs and prevents cancer. After a median of 10 years after infant immunization for HBV in a high-prevalence population, one study found that only 2% of vaccinated infants showed serology of definite or probably breakthrough HBV infection, with half of those cases in individuals born to HBeAg-positive (indicating actively reproducing virus) mothers. This was despite the very low serum anti-HBs concentrations. Occasional large increases in anti-HBs concentrations were seen, suggesting a rapid anamnestic (memory immune) response [24]. Studies of immunogenicity in HPV vaccination have shown a similar rapid decrease in serum antibody concentrations [17]. A subset of the individuals in the GARDASIL® trials was given a vaccine dose at 60 months after the start of the trial. After one week, those who had been vaccinated showed a dramatic increase in titers for antibodies to HPV type 16 (11-fold increase) and 18 (23-fold increase) while the placebo group showed much less response to the vaccine dose. In the previously vaccinated group, titers one month after the fourth dose of vaccine were higher (1.5-1.6 fold) than one month after the third dose, given at 7 months [18]. This suggests a very strong immune memory in the presence of very low serum antibody titers.

While these results are encouraging, they do not guarantee long-term protection. Merck has established a Scandinavian registry-based follow-up cohort of 5498 individuals to monitor the long-term protection of their vaccine [18]. Since these individuals began the vaccination series three years before the start of publicly available vaccinations in the United States, this cohort should hopefully give warning of any waning in vaccine protection.

Safety

The data on the safety of GARDASIL® has been reassuring [17]. However, as the vaccine enters the market and its use becomes more widespread, the possibility of observing previously unrecognized potentially serious reactions increases. The Vaccine Adverse Event Reporting System (VAERS) managed by the FDA and CDC will be used, as with all vaccines, to monitor for previously unrecognized or rare events, known adverse reactions, safety issues unique to vaccine lots, and predisposing factors for adverse reactions. In addition, the Vaccine Safety Datalink (VSD), a collaboration between the CDC and managed care organizations, will also monitor vaccine safety. With the VSD, a very large population with an annual birth cohort of over 90,000 is represented with the ability to perform controlled population-based studies on vaccine safety. The VSD will also track pregnancy outcomes for vaccinations inadvertently administered during a pregnancy [25]. Merck will also monitor vaccine safety using several studies, including the use of Scandinavian birth registries for outcomes the result of inadvertent administration during pregnancy [26].

Cost-effectiveness

Various models have been used to predict the cost-effectiveness of HPV vaccines compared with just screening, with a range of less than \$0 to \$70,000 cost per quality-adjusted life year (QALY) based on the parameters used for each model. With Markov models, which do not include the effects on transmission and herd immunity, vaccination of 12-year-old females against HPV types 16 and 18 had a cost per QALY of about \$23,000. This is substantially less than the cost per life-year saved for the pneumococcal conjugate (\$80,000) and meningococcal conjugate (\$121,000) vaccines. In all models in which it was studied, a catch-up vaccination of those over 12 years of age, including the effects of herd immunity, and the addition of coverage for HPV types 6 and 11 improved the cost-effectiveness. Some items that were not taken into account with these models were non-cervical HPV-related cancers, decreased positive predictive value of the Pap test, changes in health-seeking behavior, potential changes in sexual behavior, and negative outcomes of vaccination such as adverse reactions to the vaccine. Also unknown is if changes in screening recommendations, e.g. changing the duration between screenings or the adoption of HPV tests as the principal screening tool, will occur in the future as the result of HPV immunization [27].

Vaccine acceptance

For these vaccines to reach a large number of people, acceptance of the vaccine by health care

providers, the individual, and parents/guardians in the case of minors will all play a role. Each group has their own concerns regarding the vaccine, and thus different approaches are needed to increase vaccine acceptance within each group.

Health care providers play a large role in a patient's decision of what health treatments to pursue, thus insuring health care provider acceptance of HPV vaccines will be crucial in improving utilization of the vaccine. One study found that factors positively associated with pediatricians' intent to recommend a vaccine against HPV to 10-15 year-old patients were a higher estimate of the perceived number of sexually active adolescents in the physician's practice, a higher number of adolescents seen per week, knowledge regarding HPV, willingness to follow vaccine recommendations from important organizations and individuals, and fewer perceived barriers to vaccination. Long-lasting immunity and safety were the most important characteristics of an HPV vaccine [28]. A similar survey of family physicians noted female gender of the provider, knowledge of HPV, endorsement by professional organizations, and decreased perceived barriers to vaccination were all associated with a higher intent to recommend an HPV vaccine to patients [29]. In both studies, the physicians surveyed were more likely to recommend the vaccine to older adolescents and female adolescents. In addition, participants were more likely to recommend a vaccine against cervical cancer and genital warts versus a vaccine effective only for cervical cancer [28,29]. Another study, this one of gynecologists, found that recommendation of an HPV vaccine by the American College of Obstetricians and Gynecologists was the most important factor in intent to recommend a vaccine for HPV. Other significant positive factors were vaccine efficacy and older patient age [30].

Given this data, education of physicians can have a positive impact on vaccine acceptance. All three groups listed recommendations by their respective professional organizations (American Academy of Pediatricians, American Academy of Family Physicians, and American College of Obstetricians and Gynecologists, respectively) as critical factors in determining willingness to recommend a vaccine for HPV to their patients. Including any recommendations by these groups in provider informational materials would likely be very effective at increasing vaccine acceptance. Other items to address would include knowledge of HPV, vaccine efficacy, and the vaccine safety profile. It is interesting that all three groups were more likely to vaccinate older adolescents versus younger adolescents. Reinforcing the need to vaccinate adolescents before sexual debut and providing data on the age of sexual debut might increase acceptance of vaccinating younger adolescents as recommended by the ACIP. In addition,

both pediatricians and family physicians were more likely to vaccinate females than males. If a safe and effective HPV vaccine for males is developed and obtains approval from the FDA and ACIP, educating providers on the herd immunity effect of vaccinating males, as well as the risks of HPV-related anal and penile cancers could increase intent to vaccinate male adolescents.

Most adolescent and young adult women would be willing to receive a vaccine for HPV [31-33]. Factors associated with increased likelihood to receive an HPV vaccine include low cost [31,33,34], low risk of adverse effects [31,34], and approval or recommendation of a physician, parent, or partner [31,32,34]. Methods to reduce cost to the patient, informing the patient of the safety profile of the vaccine, and improving vaccine acceptance by physicians and parents could improve patient acceptance.

Since the targeted age of vaccination is 11-12 year-old females, parental consent, and thus parental acceptance, will have a large impact on the total utilization of any vaccine for HPV. One study of hypothetical immunization scenarios indicated that important features for acceptance of the vaccine were the severity of the infection being immunized against and the efficacy of the vaccine. Sexual transmissibility of the infection was not a significant factor in parental acceptance of a vaccine [35]. When presented with hypothetical vaccines for a variety of STIs, parents of children largely supported (85.3%-93.1% acceptance) immunization of their children for that particular STI. Factors that significantly increased the rate of acceptance were recruitment of parents from public clinics versus private clinics, parental history of an STI, increased concern of their child's risk of contracting an STI, perception that an STI diagnosis for the child would be mentally and physically severe on the child, and decreased belief that immunization for an STI would lead to unsafe sexual behaviors [36]. When questioned specifically about a vaccine for HPV, parents were generally accepting of immunizing their child [37-41]. Many factors associated with increased acceptance were similar to those with generic STI vaccine scenarios: attending urban clinics, lower level of parental education [41], parental history of genital warts [37], increased perceived risk of child acquiring HPV [37,39,41], and decreased concern that immunization against HPV would suggest parent is condoning sexual behavior [39-41]. In addition, perceived benefit to the child and society [37] and physician recommendation [37,39] were cited as increasing parental acceptance. One study found that lack of sufficient information to make an informed decision was given as a reason in 30% of parents not accepting immunization for their child [41]. Another found that 23% of parents stating they would not

approve of HPV vaccination for their child believed that their child would be more likely to have sex because of the vaccination, compared to 9% of those who would accept vaccination and 6% in those unsure of their decision to vaccinate their child [40]. Together, these studies suggest that parental acceptance of a vaccine for HPV depends on a large number of considerations, likely with different priorities for different people. Addressing these topics, especially physician endorsement, lifetime risk of HPV infection with potential outcomes, and efficacy and safety information for the vaccine, might be beneficial in increasing parental acceptance of an HPV vaccine.

Behavioral disinhibition and abstinence

As mentioned above, a significant number of parents not approving of their child receiving a vaccine for HPV stated a concern that immunizing their child would result in an increase in that child's unsafe sexual behaviors. This concept of an increase of unsafe behaviors as the result of a measure designed to increase safety has been termed "behavioral disinhibition." Some classic examples are concerns of increased drug use because of needle exchange programs and concerns of increased sex due to condom distribution programs and emergency contraception. If a vaccine for HPV were to increase unsafe sexual practices in recipients, this would definitely warrant concern over the overall health effects of the vaccine. Even if evidence indicates that behavioral disinhibition is unlikely to occur, this needs to be communicated as it may play a significant role in both parents' and providers' decision to vaccinate an adolescent.

A significant number of adolescents are having sexual intercourse: 63.1%, 51.4%, 42.8%, and 34.3% of 12th, 11th, 10th, and 9th grade students, respectively. 3.7% of high school females report having sexual intercourse for the first time before the age of 13 years (8.8% for males). 21.4%, 16.2%, 11.5%, and 9.4% of 12th, 11th, 10th, and 9th grade students, respectively, report having 4 or more lifetime sexual partners [42].

Obviously, many adolescents are having sex. The question remains as to what the major deterrents to sexual intercourse are in adolescents are. In both males and females age 15 to 17 years who have not yet had sexual intercourse, the top three main reasons selected for why they have never had sex were "Against religion or morals," "Don't want to get (a female) pregnant," and "Haven't found the right person yet." (See Table 1.) Only 9.1% of females and 12.0% of males cited "Don't want to get a sexually transmitted disease" as the main reason for never having sex. Inclusion of individuals age 18 to 19 years who have never had sex resulted in a decreased percent distribution for the choice "Don't want to get a sexually transmitted disease" [43].

TABLE 1. Percent distribution of main reason reported for never having sex in 15-17 year-olds who have not yet had sexual intercourse [43].

	Females	Males
Against religion or morals	37.5	29.3
Don't want to get (a female) pregnant	19.1	27.4
Don't want to get a sexually transmitted disease	9.1	12.0
Haven't found the right person yet	15.9	17.9
In a relationship, but waiting for the right time	6.1	4.3
Other reason	12.3	9.2

While HPV is the most common sexually transmitted disease, few teenagers have a good understanding of the virus or the diseases it causes. In a small study of female adolescents recruited in a health clinic waiting room with a mean age of 15.6, when asked to recall all sexually transmitted diseases they knew of, none mentioned HPV. Of the 85% who had had a Pap smear, only 35% knew the purpose of the Pap smear was to detect precancerous and cancerous lesions involving the cervix; none mentioned HPV in relation to the need to obtain a Pap smear [44]. Another study demonstrated that only 13% of high school seniors had heard of HPV [45]. In a separate study of adolescents recruited from urban children's hospital waiting areas, only 23% listed HPV as a sexually transmitted disease [46]. Even in adults, knowledge regarding HPV is low [44,47].

Those who decide to remain abstinent until marriage still have a sizeable risk of contracting HPV. 10.8% of high school student females report being forced to have sexual intercourse against their will (4.2% for males) [42]. In a study of sexually active women age 18 to 25 selected from the general population, 14.3% of those reporting only one lifetime vaginal sex partner tested positive for HPV [3]. In addition, HPV can be transmitted by non-penetrative sexual contact, with one study showing a 7.9% 24-month cumulative incidence of HPV infection in virginal women [48].

It seems unlikely that behavioral inhibition related to immunization against strains of HPV will be a prevalent occurrence, given an overwhelming majority of adolescents who have not yet had sex cite reasons other than concern of contracting a sexually transmitted disease as the major reason for not having sex. When one considers that many adolescents have never even heard of HPV or know that it can cause cervical cancer, this becomes even less likely. While abstinence until marriage might prevent many cases of HPV, it will not provide complete protection as evidenced by data

showing transmission of HPV through non-penetrative sexual contact, the risk of non-consensual sexual intercourse, and the rate of HPV infection in women with one lifetime vaginal sexual partner. Nonetheless, safer sexual practices, including abstinence, should not be devalued.

Education

As noted above, the knowledge regarding HPV and its complications is fairly poor among the general public. Health care providers also have their own questions and concerns regarding these new vaccines. In addition to addressing the items previously mentioned, such as general information on HPV, cervical cancer, organizations recommending immunization against HPV, and vaccine efficacy and safety, several other items should be stressed.

While the data on the efficacy of these vaccines has been remarkable, before vaccination people should understand that it is unrealistic to expect 100% coverage against the included strains. In addition, the vaccine will not protect against all strains of HPV, and thus will not prevent all cases of genital warts and cervical cancer. Because not all cases of cervical cancer will be preventable, it will be critical that women understand that obtaining regular Pap smears will still be required for cervical cancer screening.

People need to comprehend that this vaccine will not prevent infection with other STIs and will not prevent pregnancy. Thus, the continuation of other safer sex practices should be strongly encouraged. A substantial amount of misinformation regarding sexual health is presented to children, including from federally funded sexually education programs [49]. Hopefully physicians will seize the opportunity to have a discussion regarding sexual health with patients when they present to receive this vaccine.

Funding

The proposed cost for Merck's GARDASIL® is \$120 per dose, for a total cost of \$360 for the series [50], making it a sizeable financial burden. This cost also does not include charges for administration and office visits. Now that the vaccine has been added to the VFC Program, federal money will be used to provide vaccinations for all females 9-18 who are either eligible for Medicaid, uninsured, an American Indian or Alaska Native, or covered by insurance that does not include vaccinations (this last group must receive the vaccination from a Federally Qualified Health Center (FQHC) or Rural Health Clinic (RHC)) [51]. Individuals with insurance that has a high deductible and includes coverage for immunizations, and individuals with "buyer's club" programs that do not specifically state that vaccinations are not covered, are

not eligible for the VFC Program [52]. The vaccine is expected to be available through the VFC Program once a price agreement has been reached between Merck and the federal government. Merck has also announced the creation of a patient assistance program that will provide free vaccines for adults who are uninsured and unable to afford vaccines [53].

Once a vaccine is recommended by the ACIP, most private insurers cover the vaccine. A number of private insurers have already stated that they are covering or intend to cover GARDASIL®. Nationally this includes Aetna [54], WellPoint [55], and Kaiser [56]. In Wisconsin, there have been reports that Physicians Plus, Blue Cross Blue Shield, and Humana will cover the vaccine.

Wisconsin State statute states that private insurers, with some exceptions, are mandated to cover "appropriate and necessary immunizations, from birth to the age of 6 years" without subjecting the immunization to any co-payment [57]. The "appropriate and necessary" wording leaves some interpretation. That the statute does reference the US public health service may suggest ACIP recommended immunizations. However, since the age limit is 6 years, this statute will not apply to GARDASIL®. With the increasing emphasis on adolescent immunizations (Tdap, MCV4, and now HPV), consideration for revision of this statute may be appropriate.

Section 317 of the Public Health Services Act provides federal grants to assist in vaccinating individuals who otherwise do not have coverage for vaccinations. Section 317 Funding has not been maintained with respect to the increase in cost of immunizations [58]. The 2007 President's budget to Congress included a \$100 million cut in Section 317 funding. With this budget was included a proposed addition of \$140 million to the VFC Program to allow underinsured children, those with health insurance lacking vaccination coverage, to receive VFC funded vaccines at public health clinics in addition to the FQHCs and RHCs currently required [59]. While this might improve access for VFC qualified individuals (who are already guaranteed federally funded vaccines), it will decrease vaccination funding for those who are ineligible for VFC and do not have insurance that covers immunizations. If these changes are enacted, little federally funding for the new and relatively expensive GARDASIL® will be available to those who are underinsured but not eligible for VFC.

Access

In addition to funding, the willingness and ability of providers to administer the vaccine will affect access to this new vaccine. In addition to the groups traditionally thought of as providing vaccinations (family physicians, pediatricians, and general internists), there is the

potential for several new groups to assist in distributing the new HPV vaccine.

Obstetricians/gynecologists are in an excellent position to increase access. Not only is their field tailored to the reproductive and sexual health of women, but many have seen a significant amount of the morbidity associated with HPV and are thus could provide a personal perspective on the risks associated with HPV. However, the VFC Program requires that providers follow the ACIP immunization recommendations in order to be eligible as a VFC provider, indicating that they must be willing to provide all of the VFC vaccines [60]. Family planning clinics would also be able to increase access to this vaccine; however, they would be subject to the same requirement.

All states have statutes that allow minors to obtain treatment for sexual and reproductive health issues, such as STIs, without parental consent [61]. There is also precedent for minor consent to immunization of STIs. As of 1997, 9 states had legislation that allowed minors to consent for HBV vaccination at family planning and STD clinics, of which Wisconsin was not one [62]. Wisconsin statute reads “a physician may treat a minor infected with a sexually transmitted disease or examine and diagnose a minor for the presence of such a disease without obtaining the consent of the minor’s parents or guardian” [63]. While the intent of the law may have been that minors can consent for all STI related medical care, the letter of the law is specific for diagnosis and treatment. In addition, the statute does not state a minimum age for consent, with the exception of testing and treatment for HIV, which is set at 14 years [64]. One source states that there has not been a single case of a state or federal court ruling that a minor less than 12 years of age can consent to his or her own medical care [65]. In light of this, it seems unlikely that females 9 to 11 years of age would be able to consent to immunization even if state statute was interpreted or modified to include immunization against STIs.

With the large range in age that the vaccine can be administered, the initial rollout could cause shortages if supply is not large enough. Assuming an optimistic 20% uptake in the first year, at least 21.6 million doses will be needed, which Merck has assured that they will be able to meet [66].

Requirements

School mandated immunizations have been shown to substantially increase immunization rates [67]. Probably the main reason for this effect is that parents who are less pro-active regarding their children’s health are forced to make a decision regarding vaccination. It also assists by providing more equitable care for those who do not have routine access to medical services and

those whose providers are not as pro-active or informed regarding recommended childhood vaccinations.

Some individuals and groups have come out against requiring HPV immunization for school, stating the parents should be the ones to decide when their children should be vaccinated. Most of these groups do support the vaccine itself, evidenced by statements such as that there are “strong reasons why even someone practicing abstinence and fidelity may benefit from HPV vaccines” by the Family Research Council. The opposition to school requirements is based mostly on the previously mentioned concern of behavioral disinhibition and the fact that HPV is not transmitted from casual school contact [68]. The issue of behavioral disinhibition has been discussed in depth above. Regarding the lack of casual contact transmission for HPV, there is a precedent for mandating school immunization against such an agent: HBV immunization. HBV is transmitted through contact with blood from, having sex with, or being born by an infected individual. While it can be transmitted through personal care items such as toothbrushes and razors, none of the above exposures fall into the category of “casual contact” [69]. Though not widely considered as such, vaccines for HBV were the first STI vaccine. HPV has drawn more attention since it is almost exclusively transmitted by sexual intercourse.

There is also precedence for vaccination for public health reasons, not just the health of the student, which goes beyond the concept of providing herd immunity for school children. When rubella immunization requirements were put in place, the primary goal was not prevention of disease in school children; it was to prevent congenital rubella infection [70]. Thus, it would appear that requiring immunizations can be justified on the basis of public health, not just the benefit to the vaccinated individual.

For the currently required school immunizations in Wisconsin (4 DTP/DTaP/DT/Td, 4 Polio, 2 MMR, 3 Hep B, 1 Var) [71], waivers are available for medical, religious, or personal conviction reasons [72]. These exceptions would be applied to any new mandated vaccinations, including HPV vaccination, allowing parents who are concerned regarding behavioral disinhibition to opt out of having their child vaccinated. Before a vaccine is required for mandatory schooling, however, there should be support in place to ensure that it does not become a financial burden on students and their families. Unless drastic increases in immunization funding occur, the state will not be able to guarantee that every individual who does not meet VFC criteria and does not have insurance covering vaccinations will be able afford these immunizations. Without adequate funding, it would seem irresponsible to require HPV vaccination for school children, even if all other issues are addressed.

Future Developments

Ongoing studies are assessing the efficacy and safety of GARDASIL® in males [73]. This could be especially promising for men who have sex with men (MSM) given research showing a high prevalence of HPV-related disease, including anal squamous intraepithelial lesions, precursors of anal cancer [74].

While HPV vaccines will prevent a substantial amount of HPV-related morbidity and mortality, the effects worldwide could be exponentially greater, preventing a large portion of the 470,600 yearly cases of cervical cancer [8]. The Bill and Melinda Gates Foundation has already pledged nearly \$28 million to the Program for Appropriate Technology in Health (PATH) to assist in the delivery of HPV vaccines to women in developing countries [75].

Conclusion

HPV immunization has the potential to be the greatest advance in women's health since the Pap test and the mammogram. There are also significant potential benefits for men. So far, Merck's quadrivalent HPV vaccine GARDASIL® appears very effective and safe, with ongoing studies to monitor these areas. Health care providers, parents, and individuals seem generally accepting of HPV immunization. With the recommendation of the ACIP for routine vaccination and the inclusion in the VFC Program, GARDASIL® will likely have a sizeable distribution in its first year on the market. Objections specific to this vaccine are centered on the concern of the possibility of behavioral disinhibition. While evidence does not indicate that this will be a likely or frequent occurrence, parents, providers, and organizations may not be easily swayed. Public education should include and emphasize the efficacy and safety of the new vaccines, as these have been shown to be among the most important factors for health care providers, parents, and individuals. Other items that must also be stressed are that these vaccines will not prevent all infections with HPV, Pap tests are still necessary even for those vaccinated, and that these vaccine will neither prevent infections with other STIs nor prevent pregnancy. The number of insurers covering GARDASIL® should continue to increase, and when combined with the VFC Program and Merck's patient assistance program, a substantial number of individuals should be able to obtain this vaccine. However, with the expected decrease in Section 317 funding, there will still be a sizeable portion of the population who are unable to afford immunization. This may prove to be the deciding factor in deciding whether HPV immunization is required for school.

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