Human Papillomavirus Vaccine

Report to the Minnesota Legislature 2008

Minnesota Department of Health

February 1, 2008

MINNESOTA MDH DEPARTMENT OF HEALTH

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Executive Summary

Genital human papillomavirus (HPV) is the most commonly sexually transmitted infection in the United States and around the world. An estimated 20 million Americans are currently infected, and each year, an additional 6.2 million persons ages 14 to 44 years are newly infected.

Over the last 40 years, widespread cervical cancer screening using the Pap test, along with treatment of pre-cancerous cervical abnormalities, has resulted in a marked reduction in cervical cancer incidence and mortality in the U.S. In addition, the incidence of cervical cancer and mortality from this disease in Minnesota is lower than in the U.S. as whole. Nonetheless, about 175 Minnesota women are diagnosed with this disease annually and about 45 die.

In June 2006, the Food and Drug Administration (FDA) licensed a quadrivalent HPV vaccine (Gardasil) for girls and women ages 9 through 26 years. Six months after initial distribution, 70 percent of Minnesota VFC providers had ordered HPV vaccine and 16,780 doses had been distributed (Graph 3). GlaxoSmithKline has developed a second HPV vaccine, Cervarix, and is seeking FDA licensure for women ages 10 through 55 years. With the advent of these vaccines, the 2007 Minnesota Legislature directed the commissioner of health to prepare a report as to whether HPV vaccine should be made mandatory statewide as part of Minnesota's School Immunization Law.

As directed, this report reviews relevant data on the epidemiology of HPV and cervical cancer, the efficacy and safety of HPV vaccine, the status of federal immunization recommendations, and the cost of HPV vaccine. It concludes that a statewide mandate of human papillomavirus (HPV) vaccination as part of the School Immunization Law is not warranted at this time. The primary reasons are that more time is needed - for providers to routinely stock and offer HPV vaccine, for the public to understand and accept it, for manufacturers to ensure production of adequate and ongoing supplies of vaccine, for funding streams to be more dependable and consistent, and for more children to be vaccinated so the responsibility for vaccination doesn't fall too heavily on schools. In addition, the incidence of cervical cancer in Minnesota is relatively low because of Minnesota's effective screening programs.

Conclusion:
A statewide mandate of human papillomavirus (HPV) vaccination as part of the School Immunization Law is not warranted at this time.

This report, therefore, recommends that rather than mandating HPV vaccine at this time, MDH and healthcare providers:

- Continue to educate the public about the causes, prevention, and early detection of HPV and cervical cancer.
- Continue to actively educate adolescents, preadolescents, and their parents about the advantages and limitations of the HPV vaccine, so these individuals can make an informed decision about vaccination.
- Continue to stress the importance of Pap tests for cervical cancer screening at the same time information is given out about the vaccine.

This report was prepared with the assistance and input of the Minnesota Immunization Practices Advisory Committee (MIPAC), members of the 2005 cervical cancer elimination study and Minnesota Department of Health (MDH) immunization staff.

Background

During the 2007 Minnesota legislative session, legislation passed that directed the commissioner of health to:

> "[R]econvene the cervical cancer elimination study required under Laws 2005, First Special Session chapter 4, article 6, section 52, to conduct a study, in collaboration with the Minnesota Immunization Practices Advisory Committee, on the human papilloma virus vaccine, including, but not limited to, the following:
> (1) the risks and benefits of the human papilloma virus vaccine;
> (2) the availability and effectiveness of the vaccine;
> (3) the extent to which health plan companies cover the cost of this vaccination; and
> (4) ways to cover the cost of vaccination for persons without coverage.
> The commissioner shall submit a report to the legislature by February 1, 2008, on the findings of the study and recommendations as to whether the human papilloma virus vaccine should be made mandatory statewide." (MN Session Laws 2007, Chapter 147, Art. 10, sec. 14)

As directed by the Legislature, the Minnesota Immunization Practices Advisory Committee (MIPAC) met to review human papillomavirus (HPV) vaccine issues on October 1, 2007. Members of the Cervical Cancer Elimination Study were also consulted throughout the Fall of 2007 in writing this report.

As summarized in this report, MIPAC, members of the Cervical Cancer Elimination Study, and MDH immunization staff reviewed the epidemiology of the human papillomavirus (HPV) and cervical cancer, the efficacy and safety of the HPV vaccine, federal HPV immunization recommendations, implementation issues, and the cost of the vaccine. Based on this review, they made a recommendation not to mandate HPV as part of the School Immunization Law (Minn. Stat. §121A.15) at this time.

Note: This report discusses both the quadrivalent (Gardasil) and bivalent (Cervarix) HPV vaccines. The quadrivalent vaccine has already been licensed by the Food and Drug Administration (FDA) and the bivalent vaccine is expected to receive FDA licensure approval in 2008. This report makes no recommendation on which vaccine is preferred.

Epidemiology of Human Papillomavirus (HPV)

What is HPV?

Human papillomavirus is the name given to a group of viruses that includes more than 100 different types. More than 40 of these viruses are sexually transmitted (this is referred to as genital HPV infection). About 30 of these HPV types are called "high-risk" (e.g., HPV 16 and 18); they may cause abnormal Pap tests and can lead to cancer of the cervix, vulva, vagina, anus, or penis. Others are called "low-risk" HPV types (e.g., HPV 6 and 11) and may cause genital warts and mild Pap test abnormalities.

Genital HPV infection is the most commonly sexually transmitted infection in the United States and around the world. An estimated 20 million Americans are infected, and each year an

additional 6.2 million persons ages 14 – 44 years are newly infected.[1] More than half of all sexually active people will be infected with HPV at some time in their lives. By age 50, at least 80 percent of women will have acquired HPV infection.[2] Studies show that prevalence is highest among sexually active females less than 25 years old and then decreases with increasing age.[3]

Data from a 2003-04 multistate, clinic-based study of sexually active women in the United States indicated that prevalence of HPV infection was highest among those age 14 to 19 years.[4] Studies of new HPV infection demonstrate that acquisition occurs soon after sexual debut.[5] In a prospective study of college women in the United States, the cumulative probability of incident (new) HPV infection was 38.9 percent by 24 months after first sexual intercourse. Of all HPV types, HPV 16 acquisition was highest (10.4 percent) followed by HPV 18 (5.6 percent).[6] (The HPV vaccines discussed later in this report provide protection against these two HPV types.)

The majority (90 percent) of HPV infections cause no symptoms and are successfully eliminated by the body's natural defenses. However, in some individuals HPV infection is not readily resolved. About 10 percent of women infected with HPV develop persistent HPV infection[7] and some persistent infections later develop into cervical cancer in women. In 2007, an estimated 11,150 women in the United States will be diagnosed with invasive cervical cancer and 3,670 will die from this disease.[8] In addition, for every woman diagnosed with invasive cervical cancer, another seven are likely to have been diagnosed with *in situ* disease -- that is, non-invasive cancer of the cervix.[9] Data on these earlier stage, *in situ*, pre-cervical cancers are not generally collected by cancer registries and therefore do not appear in cancer statistics. However, they reflect the scope of HPV infection in the population. Less common are other types of anogenital cancers, which occur in both sexes.

In the United States, mortality from cervical cancer dropped 70 percent between 1950 and 1970 and 40 percent between 1970 and 1999.[10] This improvement has been attributed largely to screening with the Pap test.

Genital warts in both men and women are also common manifestations of certain HPV types. In the United States, an estimated 1 percent of adolescents who are sexually active will have clinically apparent genital warts,[11] 90 percent of which are the result of infection of HPV types 6 and 11. These lesions do not lead to cancer and will often resolve on their own, but they do recur and can cause abnormal Pap tests that require follow-up.

Certain low risk HPV types (e.g., types 6 and 11) are also responsible for recurrent respiratory papillomatosis (RRP). This is a rare disease in which obstructive papillomas (non-cancerous tumors) form on the larynx and vocal cords, causing considerable illness in affected infants and young children (e.g., repeated surgeries for removal of the papillomas). There is considerable evidence that RRP in children results from transmission of HPV from mother to child. There is also an adult-onset form of RRP, but less is known about its incidence and prevalence in adults. There are approximately 20,000 cases of RRP a year in the United States.[12]

How does HPV spread?

Genital HPV infection is primarily spread through sexual contact, often through intercourse. Since most HPV infections have no signs or symptoms, most infected persons are unaware they are infected and can transmit the virus to a sex partner. In most studies of HPV prevalence and incidence, the most consistent predictors of infection have been measures of sexual activity, most

importantly the number of sex partners. For example, one study found that women ages 18 to 25 who had more sex partners had higher risk of having HPV infection (Table 1). [13]

Table 1

Number of Lifetime Sex Partners of Women ages 18-25	Percentage With HPV Infection
one partner	14.3 %
two partners	22.3%
three partners	31.5%

(Note: condoms will decrease the risk of HPV transmission, but not eliminate it.)

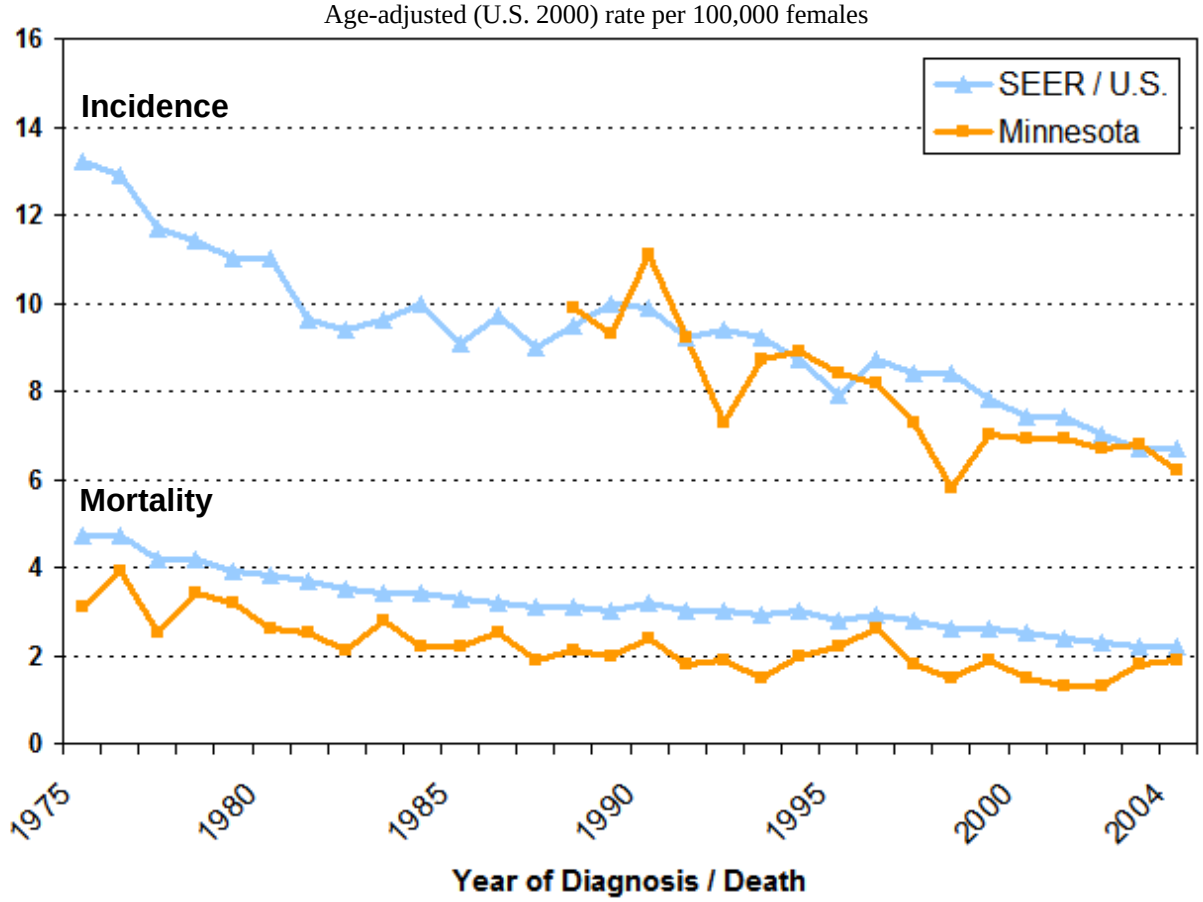
Transmission of HPV through other types of genital contact in the absence of intercourse is less common but does occur. Genital HPV infection can also be transmitted by nonsexual routes, such as transmission from a mother to a newborn baby, but this is rare.

Minnesota-specific disease information

The incidence of invasive cervical cancer and mortality from this disease is lower in Minnesota than in the U.S. as a whole[14] (Graph 1, Graph 2) and the death rate from cervical cancer in the United States is among the lowest in the world. [15] Moreover, in 2003, Minnesota ranked 32nd of 39 states reporting cervical cancer death rates and 33rd of 45 states reporting cervical cancer incidence rates (ranked highest to lowest) .[16]

Graph 1: Trends in Cervical Cancer in Minnesota and the U.S.

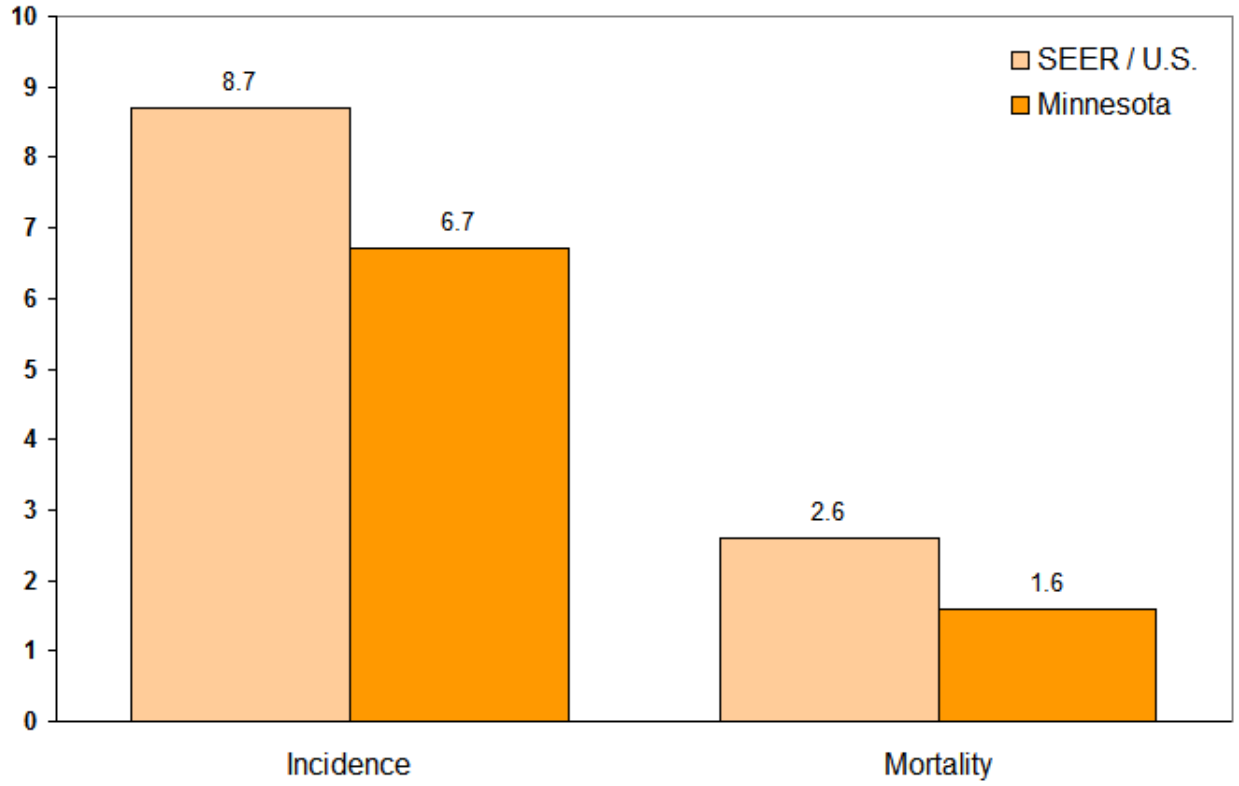
Age-adjusted (U.S. 2000) rate per 100,000 females



Source: Minnesota Cancer Surveillance System (Nov 2007) and *SEER Cancer Statistics Review, 1975-2004*. SEER incidence is for the 17 SEER Regions; mortality is for the entire U.S. N is the total number of cases and deaths in Minnesota over the five-year period.

Graph 2: Cervical Cancer in Minnesota and the U.S., 2000-2004

Age-adjusted (U.S. 2000) rate per 100,000 females



Source: Minnesota Cancer Surveillance System (Nov 2007) and *SEER Cancer Statistics Review, 1975-2004*. Minnesota rates are for all races combined. SEER incidence is for white women, including Hispanic white women, in the 9 SEER Regions covering about 10% of the US population; national mortality is for the US white population.

(SEER: Surveillance, Epidemiology and End Results. The SEER Program is run by the National Cancer Institute)

Cervical cancer control in Minnesota is highly successful due to our state's effective screening programs.[17] Nonetheless, each year about 175 Minnesota women are diagnosed with this disease and about 45 die.[18] The prevalence of HPV infection in Minnesota is unknown.

Women of color in Minnesota are two times more likely to be diagnosed with cervical cancer than non-Hispanic white women and three times more likely to die from the disease.[19] There is indirect evidence that this disparity is due to less effective screening among women of color. In addition, non-Hispanic white women living outside of the seven-country Twin Cities metro area had a 30 percent increased risk of being diagnosed with and dying from this disease than non-Hispanic white women living in the metro area during 1998-2002.[20] As stated in the 2005 Cervical Cancer Control in Minnesota report, the reason for these disparities cannot be determined. They may result from limited access or utilization of cervical cancer screening, poorer quality screening, or a lower likelihood of receiving timely and recommended treatment. Further study is needed to determine the reason for this disparity.

Minnesota does not collect information on the incidence or prevalence of genital warts because it is not a reportable disease. However, it is estimated that there are 1 million new cases of genital warts each year in the United States.[21]

HPV Vaccine

Efficacy

On June 8, 2006, the Food and Drug Administration (FDA) licensed a HPV quadrivalent vaccine called Gardasil manufactured by Merck for girls and women ages 9 through 26 years. This vaccine is called a quadrivalent vaccine because it targets four types of HPV. The two that most commonly cause cervical cancer, types 16 and 18, and the two that cause the majority of genital warts, types 6 and 11. HPV 16 and 18 are responsible for 70 percent of cervical cancer.[22] Approximately 90 percent of genital warts are associated with types 6 and 11.[23]

In clinical trials of over 11,000 females from North America, South America, Europe, Australia, and Asia, a three-dose series of the quadrivalent vaccine was been shown to be highly effective in young women who have not been previously exposed to HPV types 6, 11, 16, and 18. The vaccine was nearly 100 percent effective in preventing cervical, vulvar, and vaginal precancers caused by HPV types 16 and 18 and nearly 100 percent effective in preventing genital warts caused by HPV types 6 and 11.[24,25,26,27,28,29]

GlaxoSmithKline has developed another HPV vaccine, Cervavix, and is seeking FDA licensure for women ages 10 through 55 years. It is possible that this product will be available in 2008. This vaccine is called a bivalent vaccine because it only protects against two types of HPV: types 16 and 18. It does not protect against genital warts caused by viruses 6 or 11. As with Gardasil, studies in females show Cervarix to be almost 100 percent effective against HPV types 16 and 18 precancers.[30]

Ongoing studies from both manufacturers are also showing that these vaccines may offer some cross protection against infections caused by HPV types 31, 45, and 52, which together cause an additional 12 percent of cervical cancers.[31] The full impact of these data need further evaluation, which is underway.

In more recent studies since licensure of the quadrivalent vaccine, researchers are finding a decrease in Pap smear abnormalities among women vaccinated with this vaccine who had no previous history of HPV infection.[32] This has the potential to impact the cost of cervical screening programs because less follow-up will be needed, thus adding to the importance of vaccinating females before they become sexually active.

Limitations of HPV vaccines

Neither of the vaccines will treat an existing HPV infection. In addition, the vaccines will not protect against disease and infection caused by HPV types not included in the vaccines, though they are showing some possible cross protection against them. Since these are new vaccines, the length of vaccine protection (immunity) is also not known. So far, studies have found that vaccinated persons are protected for five years.[33] Ongoing research is being done to find out how long protection will last and if a booster dose will be needed.

Neither of the vaccines is licensed for males. Gardasil is only recommended for females ages 9 through 26 because the vaccine was only extensively tested in that age group. However, the manufacturer is conducting Gardasil studies in boys and men, as well as in women older than 26 years of age. The FDA will consider licensing Gardasil for these other groups when there is adequate data to show that it is safe and effective for them. Recently, the first efficacy study of Gardasil was conducted in 3,800 women ages 24 to 45 years. In the study, the vaccine was

shown to prevent 91 percent of cases of persistent infection, minor cervical abnormalities, and pre-cancerous and genital warts caused by the four strains of the virus in Gardasil.[34] The manufacturer of Cervarix hopes to license the vaccine for women ages 10 - 55 years.

Federal vaccine recommendations

In June 2006, the federal Advisory Committee on Immunization Practices (ACIP) recommended routine vaccination of females age 11 – 12 years with three doses of quadrivalent HPV vaccine (Gardasil). These recommendations were published in March 2007. The ACIP also recommended catch-up vaccination of females age 13 – 26 years who have not been previously vaccinated or who have not completed the full series. The ACIP also stated that the vaccine could be given as young as age 9 years, noting that "ideally, vaccine should be administered before potential exposure to HPV through sexual contact; however, females who might have already been exposed to HPV should be vaccinated." [35]

The ACIP based their recommendations on studies that support the following information.

- Quadrivalent HPV vaccine in adolescents is safe and effective.
- Higher antibody titers are achieved after vaccination at age 11-12 years compared to females ages 15-26 years.
- Data on HPV epidemiology is showing high incidence of disease at age of sexual debut in the United States.
- There is a high probability of HPV acquisition within several years of sexual debut.[36]

ACIP also stressed that providers should counsel women to continue routine Pap tests. This is to identify and follow up on abnormal smears caused by other HPV types or caused by vaccine-related HPV types that sexually active women might have been exposed to prior to vaccination.

The American College of Obstetricians and Gynecologists published their HPV immunization recommendations in September 2006. They coincide with ACIP recommendations. Also, the American Academy of Pediatrics (AAP) published matching recommendations in September 2007.

Implementation of vaccine recommendations

It usually takes at least two years from the time a vaccine is licensed for all providers to incorporate it into their practice. Uptake of a new vaccine (i.e., adoption into medical practice and acceptance by the public) is often slow and relies on certain infrastructures to be in place. These include the publication of national recommendations, the manufacture and widespread distribution of the vaccine, and the resolution of reliable vaccine financing and reimbursement issues.

The process of developing a national vaccine recommendation usually begins before the product is licensed; however, no official recommendation is made until after licensure. The process includes a review of epidemiology of the disease, the short term and long term efficacy of the vaccine, safety and cost/benefit of the vaccine, FDA licensure constraints (e.g., age restrictions), and provider and public acceptance.

National vaccine recommendations are always made by the federal Advisory Committee on Immunization Practices (ACIP), a group appointed by the Centers for Disease Control and

Prevention (CDC) and the Department of Health and Human Services to advise them on how vaccines should be used. This advisory group consists of professionals from differing disciplines, e.g., pediatrics, adult internal medicine, academic research programs, epidemiologists, adolescent medicine, etc. If the vaccine is for children and/or adolescents, the American Academy of Pediatrics and the American Academy of Family Physicians will also issue national recommendations. Other prominent national groups that may also issue recommendations or policies for vaccine use include, but are not limited to, the American College of Obstetricians and Gynecologists (ACOG), the American Medical Association (AMA), American College Health Association (ACHA), or the American College of Physicians (ACP).

The ACIP, which meets three times a year, usually makes an official recommendation at a meeting just after a vaccine is licensed by the FDA. These national recommendations become the nationally accepted medical standard for vaccine use and are published in the CDC's Mortality and Morbidity Weekly Review (MMWR). It takes 18 to 24 months from the time a product is licensed to the publication of recommendations, depending on when licensure occurred and when advisory groups meet. Most providers wait for national recommendations before beginning to use a new vaccine in their practice. The reason is two-fold:

- to receive detailed direction for who should receive the vaccine and how to use it; and
- to ensure that major insurers will cover the cost of vaccination, which they usually do once recommendations are published.

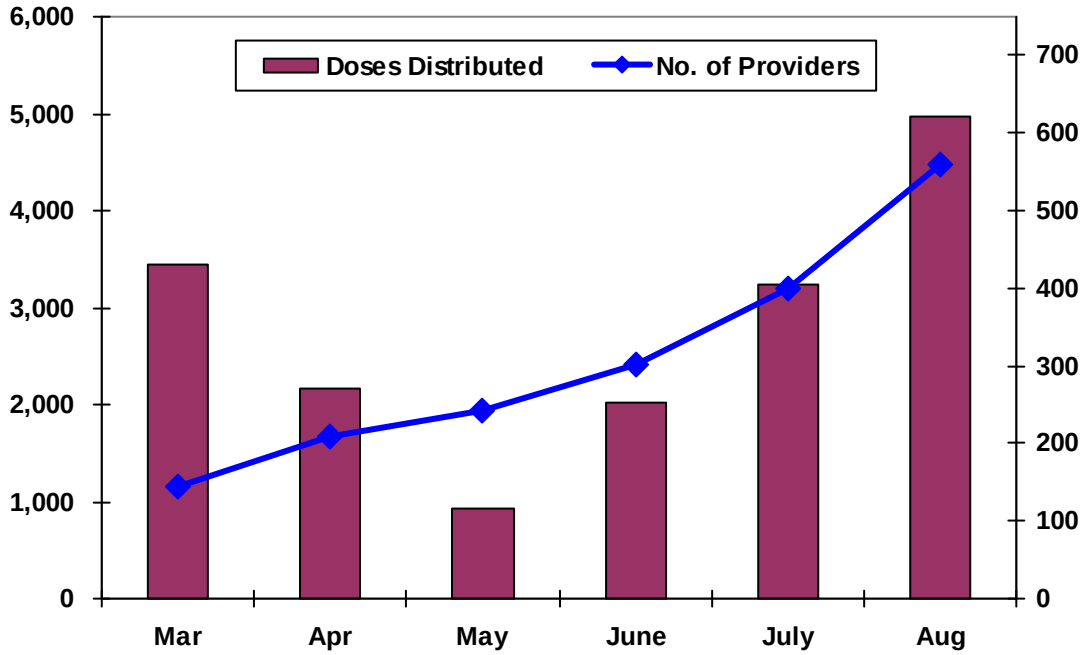
In the private sector, vaccine distribution can begin immediately following licensure of a vaccine product, even before recommendations are published; however, providers must have enough capital to purchase sufficient product in order to implement vaccination within their practice. Thus, a provider would be purchasing the vaccine before any guarantee of reimbursement for the vaccine or administrative cost. In the case of HPV vaccine, this amounts to $120 per dose. Usually providers wait for the availability of public sector vaccine through the Vaccines for Children program (VFC) before implementing a full vaccination program in their clinic. This is done to reduce the tension of providing vaccine to some children (those privately insured) and withholding vaccine to other children (those using the VFC program) and to ensure reimbursement.

Public sector vaccine distribution does not occur until the ACIP votes to include the vaccine in the Vaccines for Children (VFC) program as a resolution (codification of the ACIP recommendation) and the CDC completes negotiation of a federal contract with the manufacturer. After the CDC negotiates a price, CDC must secure additional federal funding for states to use to purchase the vaccine. In the case of HPV vaccine, public distribution through the VFC program did not begin until seven months after the HPV recommendation was made by ACIP (June 2006 to February 2007).

At MDH, new vaccine implementation includes the following activities: incorporation of the vaccine into the Minnesota VFC distribution process, adoption of national recommendations by the Minnesota Immunization Practices Advisory Committee (MIPAC) into the annual Minnesota immunization schedule, revision of all immunization tools and educational pieces used by healthcare providers and MDH, and informational updates to all immunizing providers. For HPV, all of these activities were initiated within months of ACIP approval and continue to the present.

Since February 2007 when MDH received their first shipment of HPV vaccine, uptake by Minnesota providers has been steadily growing. (Uptake refers to how fast the vaccine is incorporated into a provider's practice.) Six months after initial distribution, 70 percent of Minnesota VFC providers had ordered HPV vaccine and 16,780 doses had been distributed (Graph 3). MDH staff continues to evaluate vaccine uptake and status of funding. We are also exploring ways to increase vaccine uptake, such as reaching out to nontraditional providers who work with older adolescents and identifying ways to reduce health disparities related to accessing the HPV vaccine. For example, recently, MDH began working with nine Minnesota health plans that contract with DHS to provide primary care to persons enrolled in MnCARE and Medicaid. The health plans have developed some strategies to increase HPV vaccination rates including dissemination of informational materials (attachment A).

Graph 3: Uptake of HPV Vaccine in Minnesota, 2007



Implementation of the HPV vaccine is well underway but not complete. As stated previously, it usually takes about two years from the time a product is licensed for all providers to incorporate a new vaccine recommendation into their practice. This is true for HPV vaccination activities as well.

Vaccine safety

Background

Safety monitoring for a new vaccine is a part of its implementation. Safety is monitored in the clinical trials before licensure and once the vaccine is licensed, monitoring continues through the federal Vaccine Adverse Event Reporting System (VAERS). VAERS is a passive reporting system to which healthcare providers are required by federal law to report adverse events following vaccination, regardless of any known association to the vaccine. In addition, anyone can report an adverse event to VAERS; you do not have to be a healthcare provider. VAERS is designed to operate as an early warning system, primarily for generating hypotheses about possible new vaccine adverse events or changes in frequency of known ones. Testing for

causality is not possible with VAERS, thus VAERS cannot be used to establish a causative link between a vaccine and an event.

If a pattern of events is detected through VAERS, researchers at the CDC Vaccine Safety Office conduct further evaluation using the Vaccine Safety Datalink (VSD). The VSD is a collaborative project with several private health maintenance organizations around the country developed to more broadly review patterns of adverse events following vaccination. Because the VSD offers a database of over nine million medical records, researchers can compare and contrast data to look for rare and serious side effects following vaccination.

Pre-licensure safety data for Gardasil
Before it was licensed, Gardasil's safety was studied in seven clinical trials in over 11,000 females ages 9 through 26 years. The most common adverse events were minor and included redness, pain, and swelling at the injection site. There were a total of 10 deaths during the trials. These deaths were found in both the placebo group and the vaccine group. After close review and evaluation, none of the deaths were found to be vaccine related.[37]

Post-licensure safety data for Gardasil
Since it was licensed in 2006, more than 9 million doses of Gardasil vaccine have been distributed and its overall safety profile has not differed greatly from its original safety profile. Dizziness, fainting, and injection site pain have been the most commonly reported adverse events following vaccination. Among adolescents, dizziness and fainting are common following vaccination regardless of vaccine type; however, reports of dizziness and fainting have risen with the introduction of Gardasil. As a result, the recommendation to monitor vaccinees for at least 15 minutes following vaccination has been re-emphasized to healthcare providers.

As of September 30, 2007, just over 4,000 adverse events reports related to Gardasil have been submitted to VAERS. Some of the reports have involved Gardasil given to persons beyond the age for which the vaccine is licensed.[38] Of these, approximately 90 percent occurred in females who received only Gardasil vaccine. Slightly less than six percent of these reports were considered serious. This is less than the overall average of reported serious events for other vaccines, which usually range between 10-15 percent of the total reports received by VAERS. The reports of serious events related to Gardasil include nausea and vomiting, fever, headaches, and a neurological illness called Guillian-Barre syndrome (GBS). GBS is a neurological condition causing progressive weakness or paralysis starting in the lower body and moving upward. In more severe cases, a person's breathing muscles may be affected, requiring mechanical ventilation until the condition begins to reverse downward. Since Gardasil's licensure, there have been 17 VAERS reports of GBS filed and six cases have been confirmed. Of the six confirmed cases, five had also received meningococcal vaccine for which there is ongoing evaluation of a possible GBS association. Based on vaccine distribution data (9 million doses), 17 cases of GBS would be expected to occur by chance alone. At this point, there can be no determination of whether Gardasil increases the risk of GBS following vaccination because the incidence of GBS is so small it is very difficult to determine causation.[39] Follow-up is continuing.

There have been nine deaths reported to VAERS following vaccination with Gardasil; however, only three of these can be confirmed and they are being extensively studied. One report was actually a death due to influenza complications. Another was in a female on oral contraceptives

who died as a result of a blood clot, which is a known side effect of oral contraceptive use. The third death was due to a heart disorder for which the cause is unknown.[40]

Overall, VAERS reports have not detected any patterns or signal events that would prompt broader investigation or utilization of the Vaccine Safety Datalink.

HPV vaccine and pregnancy
Because HPV vaccine is recommended to women who are of childbearing age, pregnancy during the course of vaccination is a possibility. Gardasil is not recommended for persons who are pregnant; however, it's very possible for women who get vaccinated to subsequently find out they were pregnant at the time of vaccination. Because of this, the manufacturer has established a pregnancy registry in order to more closely follow the outcome of these pregnancies. In clinical trials, the data showed similar outcomes for pregnancy in both the groups receiving the vaccine and the groups receiving a placebo. However, there was not enough data to determine whether the vaccine could be licensed to give during pregnancy. Research on rats with the vaccine showed that there was no evidence of harm to the fetus and no impairment of fertility to the female rat.[41]

Cost and Cost-Effectiveness of Vaccine

In the public sector, the cost of Gardasil (the currently licensed quadrivalent HPV vaccine) is $96.75 per dose. Since a woman requires three doses of the vaccine, the total cost per patient in the public sector would be $290.25. In the private sector, the cost is $120.00 per dose or $360 for a complete series. These figures do not include administrative costs.

State law requires Minnesota health insurance plans to cover HPV vaccine. Forty percent of insured Minnesotans are covered under a Minnesota health insurance plan. The law states,

> "the policy, contract, or certificate must specifically exempt reasonable and customary charges for child health supervision services and prenatal care services from a deductible, co-payment, or other coinsurance or dollar limitation requirement."[42]

Child health supervision services:

> "means pediatric preventive services, appropriate immunizations, developmental assessments, and laboratory services appropriate to the age of a child from birth to age six, and appropriate immunizations from ages six to 18, as defined by Standards of Child Health Care issued by the American Academy of Pediatrics" (Minn. Stat. § 62A.047)

Thus, Gardasil is covered under "child health supervision services."

Sixty percent of insured Minnesotans are covered by self-insurance plans that are regulated by the federal government under the Employee Retirement Income Security Act (ERISA).[43] These plans are not required to follow Minnesota law and do not have to cover immunizations. While the majority of these plans do cover Gardasil, some of them require a co-pay or include the immunization in a person's deductible. As a result, they often require the individual patient to pay for all or part of their vaccination costs. This is a growing problem in Minnesota, and

nationwide, as deductibles increase. The MDH immunization program has been hearing anecdotally that girls and women have not been able to be vaccinated against HPV because of high deductibles – sometimes as high as $2,500. Unfortunately, lack of resources does not allow MDH to fully explore the extent of this as a barrier to access of HPV vaccination.

The Minnesota immunization program is completely federally financed and receives no state funding. The Minnesota Department of Health (MDH) receives two major sources of federal immunization funds: 317 federal discretionary dollars for program and administration and VFC entitlement dollars to pay for vaccines for certain eligible individuals who cannot afford them.

MDH administers the Minnesota Vaccines for Children program (MnVFC), which covers Gardasil for eligible children through 18 years of age. MnVFC is Minnesota's expanded version of the federally financed entitlement program (Vaccines For Children program - VFC) that pays for vaccines for uninsured and some underinsured children served in Federally Qualified or Rural Health Centers (FQHC/RHC).

MDH uses discretionary 317 funding to supplement the federal VFC entitlement program. This funding is used to expand eligibility for those who could receive vaccine through MnVFC. Table 2 shows the amount of federal 317 funding awards from 1999 to projected 2008. Because Congress must reauthorize the 317 funds annually, the amount of 317 funding is uncertain each year.

For example, at the beginning of fiscal year 2007, MDH was awarded $3.8 million. In the second quarter of that year, MDH received an additional $1.1 for a total of $4.9 million in 317 funding for fiscal year 2007. In August 2007, the CDC informed Minnesota that we would receive $7.1 million in 317 funding for fiscal year 2008. However, in late October, 2007, we were informed that we would only receive $4.6 million for fiscal year 2008.

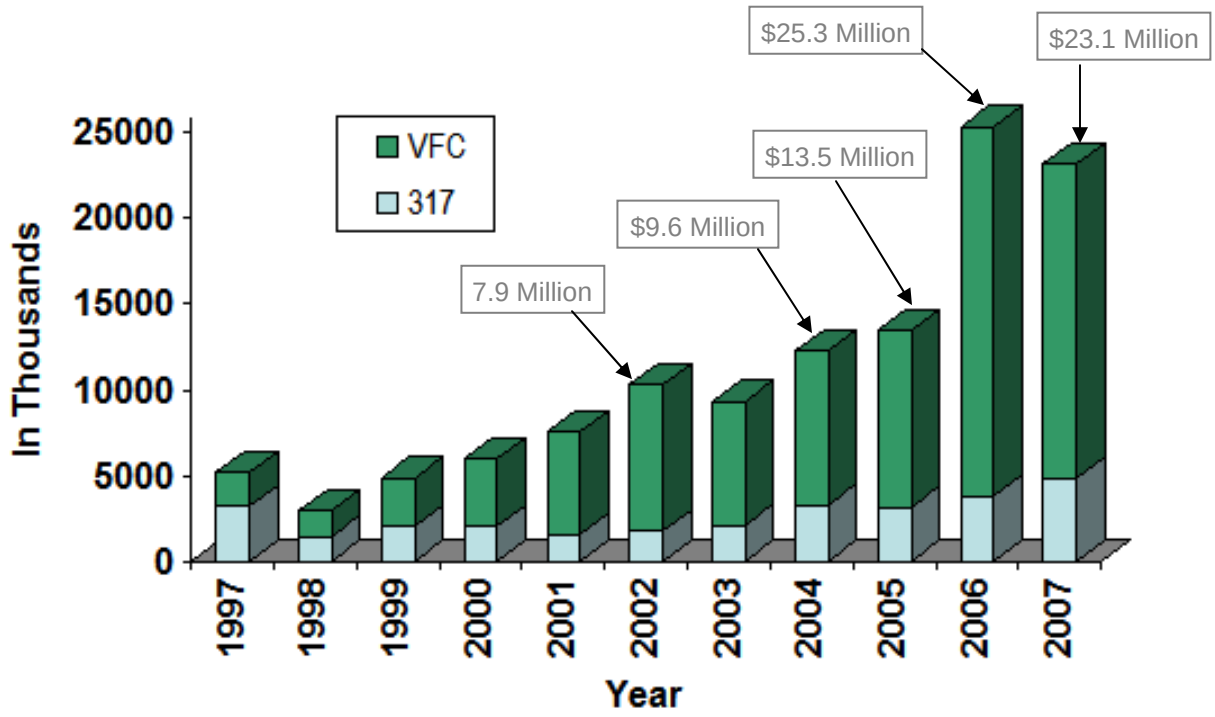
Table 2

Federal Fiscal Year	**317 Funding (*in millions*)**
1999	$2.1
2000	$2.1
2001	$1.6
2002	$1.8
2003	$2.1
2004	$3.3
2005	$3.1
2006	$3.8
2007	$4.9
2008 *(expected)*	$4.6

Specifically, MDH uses its federal 317 funds to expand VFC eligibility for free vaccines to include the underinsured: those with health insurance that does not cover the vaccine, or covers only certain vaccines, or caps coverage at a certain amount. This expanded VFC eligibility

allows underinsured children to receive vaccines in their "medical home," compared to the federal VFC program that restricts services for the underinsured to FQHC or RHC. Even though MnVFC covers some categories of underinsured persons, persons who have high deductibles are not currently included in the underinsured category. (For a complete description of MnVFC see attachment B.)

Graph 4: History of Federal Vaccine Awards Minnesota, 1997 - 2007



For HPV vaccine, MnVFC focuses on covering routine vaccination at 11-12 years of age and catch-up of 13-18 year olds who are uninsured or underinsured. MnVFC also pays for HPV vaccine for uninsured and underinsured adult women ages 19 to 26 years in public health clinics, which is a temporary catch-up program, and was planning on expanding this to Title X family planning clinics. However, since MDH was informed that our 2008 funding would be $4.6 million instead of $7.1 million, we may not be able to expand HPV coverage to Title X family planning clinics.

The Minnesota Department of Human Services (DHS) also pays for HPV vaccine for adult women through age 26 years who are enrolled in any of the DHS administered Minnesota Health Care Programs (MCHPs). This includes Medicaid (MA), MnCare, General Assistance (GA), and pre-paid Medical Account Programs (PMAP).

The MnVFC program estimates it would cost the state $522,450[44] to vaccinate one junior-high age cohort (ages 11-12 years) of underinsured children. This assumes a 5 percent underinsured rate; for example, it assumes 1,800 girls in this age cohort are underinsured under current MnVFC eligibility criteria. This amount does not include the cost of catch-up vaccination for those not in the age cohort. Each catch-up cohort (e.g., 13-year-old girls) would also cost $522,450. It is important to note that this figure is only an estimate. MDH believes that the

number of underinsured is likely to be somewhat higher. In the private insurance sector, the estimated cost to vaccinate one junior-high age cohort would be approximately $7.5 million.[45]

Conducting an in-depth study of the complete cost-benefit of the quadrivalent vaccine in junior high students in Minnesota is beyond the scope and resources of the Minnesota Department of Health. However, MDH staff have reviewed previous HPV cost studies that are summarized below.

The biggest long-term cost benefits of both the quadrivalent and bivalent HPV vaccines include reduced morbidity and mortality from cervical cancer and reductions in precancerous lesions. It is estimated that vaccinating young girls will have a substantial impact on cervical cancer rates in the U.S. population in 15 to 30 years. Shorter term benefits may include a reduced need for follow-up of precancerous lesions. In addition, the quadrivalent vaccine is expected to protect against genital warts.

Since 2003, four studies have estimated the potential cost effectiveness of HPV vaccination in the United States.[46] All four models estimated the cost per quality-adjusted life year (QALY). Cost is studied in terms of QALY to account for improvements in quality of life as well as length of life. The QALY measure is used to estimate the number of years of life (adjusted for quality of life) that would be added by the intervention – in this case the HPV vaccine. This takes into account both the quantity and the quality of life generated by a healthcare intervention.

Depending on the model used, the cost per QALY gained by routine HPV vaccination of females at age 12 years (and assuming continued Pap screening) ranged from $3,000 to $24,300. This means, for example, that it costs $3,000 to add one “quality-adjusted” life year for one person. The main reason for the discrepancies in cost-effectiveness estimates is the different set of assumptions used in each model. For example, factors such as duration of vaccine-induced protection, percent of people vaccinated (vaccine coverage), and vaccine cost all impacted the estimated cost effectiveness of HPV vaccination. It is important to note that all the studies assumed Pap screening continued at the same level as before vaccination.

The main benefit of HPV vaccination will lie in preventing cervical cancer mortality and in preventing the cost of follow-up of precancerous lesions. Even with the availability of the vaccine, women still need to receive regular screening since neither vaccine protects against all cancer-causing HPV types.

The cost of HPV vaccination is much higher that that of older routinely recommended vaccines for children (e.g., MMR, polio), but is similar to other vaccines that have been added to the childhood and adolescent immunization schedule more recently. HPV vaccination will reduce morbidity and mortality of cervical cancer increasingly over time. Additional benefits, such as herd immunity, reduced need for cervical abnormality follow-up due to decrease genital wart incidence and reduced treatment costs for respiratory papillomatosis, may be realized as well.

Recommendation and Summary of Issues

After reviewing the information presented above, MIPAC, members of the Cervical Cancer Elimination Study and MDH immunization staff concur that a junior high human papillomavirus vaccine mandate is not warranted at this time, even allowing for the usual exemptions for

medical or conscientious reasons. The following is a summary of the issues that led to this recommendation.

Considerations that are favorable for a HPV mandate

- Extensive epidemiological studies show a clear association between persistent HPV infection and cervical cancer, as well as other types of cancer.
- A mandate equalizes access across all social, economic, and racial backgrounds. Minnesota data show that cervical cancer incidence is higher in populations of color and in women with reduced access to regular healthcare. While women currently infected with HPV will not benefit from vaccination, and ongoing activities for improving healthcare access and improved screening is needed, younger females in these same populations would be vaccinated and may have a reduced risk for HPV infection and cervical cancer.
- Clinical trials and continued follow-up have determined that both the currently licensed vaccine, and the candidate vaccine, are effective in protecting females against infection with two HPV types that contribute up to 70 percent of cervical cancer for at least five years.
- Large, *pre-licensure* clinical trials of over 11,000 females have demonstrated that HPV vaccine is safe enough to be licensed.
- Vaccinating pre-adolescent girls is feasible because they are already accessing healthcare for a well-child visit and other vaccinations.
- Most health insurers are covering the cost of HPV vaccinations, although some have co-pays and high deductibles. The federal entitlement program, VFC, is providing funding for eligible children age 18 years and younger for HPV vaccination. Minnesota's expanded program (MnVFC) currently has sufficient funding to provide HPV vaccine in underinsured females through age 18 years, not including those with high deductibles and/or copays.

Considerations for not supporting a mandate at this time

- Since HPV is a newer vaccine (licensed in June 2006), mandating it would be premature at this time. There needs to be an "implementation" period before a vaccine is fully incorporated into medical practice. Time is needed for providers to routinely stock and offer the vaccine and for the public to become aware of the vaccine and accept it and understand its limitations.
- Including the vaccine in the School Immunization Law would result in a surge in vaccine use and vaccine manufacturers might not be able to keep up with the demand. The state has seen this occur in the past. For example, recently the ACIP recommended a second dose of chickenpox vaccine for all children; previously children under 13 years of age received only one dose. There is only one manufacturer of the chickenpox vaccine and demand is now exceeding supply. Shipment of the vaccine has been delayed and providers cannot get vaccine in a timely manner in order to immunize all their patients against chickenpox. MDH also had to delay implementation of the pneumococcal vaccine requirement in child care in 2004 because supply could not keep up with demand.
- The long-term efficacy of the vaccine is still unknown beyond the five years of ongoing studies. Will this vaccine continue to protect females at the age when sexual activity is more likely or will a booster dose be needed? Neither existing vaccines can protect against all cervical cancer and there is a concern that shifting the focus to a vaccination mandate for this vaccine might detract from the need to continue cervical screening, which is highly successful in Minnesota.

- Although the vaccines' safety record during the clinical trials is very good, large-scale safety data is still being collected. It is prudent to ensure that a mandated vaccine has a well-established safety profile in larger populations, but that data is not yet available.
- If the vaccine were mandated, MDH would want to ensure that everyone could have access to it. The mandate would be costly to the MnVFC program, whose funding is presently stable but may not be sustained. It would also be costly to some parents, e.g., if their self-insured health plan includes high deductibles that do not cover the cost of vaccines. This is a growing problem for many people who have these types of policies. If these funding streams were more consistent and reliable, more people would have access to HPV vaccine
- To reduce the compliance burden on schools, it is important to ensure that there is significant acceptance and use of a vaccine in the recommended populations before adding it to the School Immunization Law. If a majority of children are not vaccinated prior to a mandate, the primary responsibility to assure vaccination falls to the schools (rather than public health and private healthcare providers). In an era of limited school resources, this places an additional burden on schools. Since the HPV vaccine requires three doses, and it is a new vaccine, the burden on a school (and a school nurse) would be more substantial than the other vaccines that are currently included in the school law.
- Another area that has not been thoroughly explored is the requirement of a vaccine for one sex (girls) and not the other (boys). The vaccine may be licensed for boys in the future, but it is not currently licensed for them. This would require schools to have separate immunization policies for boys and girls. This one-sex requirement would also be more administratively burdensome for schools.
- Finally, the incidence of cervical cancer in Minnesota is relatively low. Because it is low, MDH and providers have time to promote both primary and secondary prevention without a mandate. Cervical cancer prevention entails both primary and secondary prevention approaches. Primary prevention measures include practices that limit sexual exposure to HPV (condoms, lifelong monogamy) and HPV vaccination. Secondary prevention efforts include cervical cytology and HPV screening as well as removal of HPV-infected precancerous lesions. Working together, these approaches can help reduce cervical cancer.

Conclusion

This report recommends that rather than mandating the HPV vaccine as part of the School Immunization Law at this time, the best use of public health resources is for MDH and providers to:

- Continue to educate the public about the causes, prevention, and early detection of HPV and cervical cancer.
- Continue to actively educate adolescents, preadolescents, and their parents about the advantages and limitations of the HPV vaccine so these individuals can make an informed decision about vaccination.
- Continue to stress the importance of Pap tests for cervical cancer screening at the same time information is given out about the vaccine.

In keeping with this recommendation, MDH has developed a HPV fact sheet for preadolescents/ adolescents and their parents (attachment C). We have posted this fact sheet on our immunization website. To encourage school nurses and providers to use it, MDH also plans to include this information in its Got Your Shots? newsletter and in mailings to school nurses. MIPAC will reconsider the recommendation to add HPV vaccine to the school law within three years.

[1] Weinstock H, Berman S, Cates W. Sexually transmitted diseases among American youth; incidence and prevalence estimates 2000. *Perpect Sex Reprod Health.* 2004;36:6- 10.
[2] Myers, E, McCrory D, Nanda K, Bastian L, Matchar D. Mathematical model for the natural history of human papillomavirus infection and cervical carcinogensis. *Am J. Epidemiol.* 2000; 151:1158-71.
[3] Centers for Disease Control and Prevention (CDC). Quadrivalent Human Papillomavirus Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR, 2007;56. RR2:4.
[4] Datta, D.S. et al. Sentinel surveillance for human papillomavirus among women in the United States, 2003-2004 [Abstract MO-306 ISSTDR]. Amsterdam;2005-2006.
[5] Winer R, Feng Q, Hughes J, O'Reilly S, Kiviat N, Koutsky A. Risk of Female Papillomavirus Acquisition Associated with First Male Sex Partner. *J Infect Dis*. 2008; 197:279-82.
[6] Winter R, Lee D, Hughes J, Adam D, Kiviat N, Koutsky L. Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students. *Am J Epidemiol*. 2003;157;218-26.
[7] Centers For Disease Control: http://www.cdc.gov/std/HPV/STDFact-HPV.htm.
[8] American Cancer Society. *Cancer Facts & Figures 2007.* Atlanta: American Cancer Society; 2007. Supplemental table *Cases and Deaths by Site, State 2007* available online at http://www.cancer.org/docroot/PRO/content/PRO_1_1_Cancer_Facts_and_Figures_Suppl_Data.asp.
[9] Michigan Department of Community Health. *Facts about Cervical Cancer.* Michigan Department of Community Health, February 2007.
[10] Ries, L.A. Eisner MP, Kosary CL, et al.: SEER Cancer Statistics Review, 1973-1999. Bethesda, Md: National Cancer Institute, 2002. http://seer.cancer.gov/csr/1973_1999/.
[11] Karlsson R, Jonsson M, Edlund K, Evander M, Gustavsson A, Bodén E, Rylander E, Wadell G. Epidemiology of genital human papillomavirus infection: a population-based study. *Sex. Transm Dis*. 1995;22:119-27.
[12] RRP Foundation at http://www.rrpf.org/whatisRRP.html.
[13] Manhart L, Holmes K, Koutsky L, Wood T, Kenney D, Feng Q, Kiviat N. Human papillomavirus infection among sexually active young women in the United States: implications for developing a vaccination strategy. *Sex Transm Dis*. 2006;33:502-8.
[14] Detailed information on cervical cancer in Minnesota can be found in the 2005 MDH report titled, Cervical Cancer Control in Minnesota: Assessing its Effectiveness with Data from the Minnesota Cancer Surveillance System. The report can be found at http://www.health.state.mn.us/divs/hpcd/cdee/mcss/documents/ccc.pdf.
[15] Curado M, Edwards B, Shin. H, Storm H, Ferlay J, Heanue M, Boyle. P. (2007) Cancer Incidence in Five Continents, Vol. IX IARC Scientific Publications No. 160, Lyon, IARC.
[16] National Cancer Institutes and the Centers for Disease Control: http://statecancerprofiles.cancer.gov/.
[17] 2005 MDH cervical cancer control in MN report
[18] Minnesota Cancer Surveillance System, cases reported as of November 2007 and deaths 2003-2006.
[19] 2005 MDH Cervical Cancer Control in Minnesota report.
[20] Id.
[21] Fleischer A, Parrish C, Glenn R, Feldman S. Patient demographics and treating physicians. *Sex Transm Dis*. 2001;28:643-647.
[22] Clifford G, Rana R, Franceschi S, Smith J, Gerald Gough, Pimenta J. Human papillomavirus genotype distribution in low-grade cervical lesions: comparison by geographic region and with cervical cancer. *Cancer Epidemiol Biomarkers Prev*. 2005;14:1157-1164.
[23] Greer C, Wheeler C, Ladner M, Beutner K, Coyne M, Liang H, Langenberg A, Yen T, Ralston R. Human papillomavirus type distribution and serological response to HPV type 6 virus-like particles in patients with genital warts. *J. Clin Microbiol* 1995;33:2058-63.
[24] Villa L, Costa R, Petta C, Andrade R, Ault K, Giuliano A, Wheeler C, Koutsky L, Malm C, Lehtinen M, Skjeldestad F, Olsson S, Steinwall M, Brown D, Kurman R, Ronnett B, Stoler M, Ferenczy A, Harper D, Tamms G, Yu J, Lupinacci L, Railkar R, Taddeo F, Jansen K, Esser M, Sings H, Saah A, Barr E. Prophylatic quarivalent human papilloma (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young woman: a randomized double-blind placebo-controlled mulitcenter phase II efficacy trial. *Lancet Oncol* 2005;6:271-8.
[25] Villa L, Ault K, Giuliano A, Costa R, Petta C, Andrade R, Brown D, Ferenczy A, Harper D, Koutsky L, Kurman R, Lehtinen M, Malm C, Olsson S, Ronnett B, Skjeldestad F, Steinwall M, Stoler M, Wheeler C, Taddeo F, Yu J, Lupinacci L, Railkar R, Marchese R, Esser M, Bryan J, Jansen K, Sings H, Tamms G, Saah A, Barr E. Immunological responses following administration of a vaccine targeting human papillomavirus Types 6, 11, 16, and 18. *Vaccine* 2006;24:5571-83.

[26] Villa L, Costa R, Petta C, Andrade R, Paavonen J, Iversen O, Olsson S, Høye J, Steinwall M, Riis-Johannessen G, Andersson-Ellstrom A, Elfgren K, Krogh G, Lehtinen M, Malm C, Tamms G, Giacoletti K, Lupinacci L, Railkar R, Taddeo F, Bryan J, Esser M, Sings H, Saah A, Barr E. High sustained efficacy of a prophylactic quadrivalent human papilloma virus 6/11/16/18 L1 virus-like particle vaccine through 5 years of follow-ups. *Br J Cancer* 2006;95:1459-66.
[27] Siddiqui MA et all. Human papillomavirus quadrivalent (types 6, 11, 16, 18) recombinant vaccine (Gardasil). *Drugs*. 2006;66(9):1263-71.
[28] Olsson S, Costa R, Petta C, Andrade R, Malm C, Iversen O, Høye J, Steinwall M, Riis-Johannessen G, Andersson-Ellstrom A, Elfgren K, von Krogh G, Lehtinen M, Paavonen J, Tamms G, Giacoletti K, Lupinacci L, Esser M, Vuocolo S, Saah A, Barr E.. Induction of immune memory following administration of a prophylactic quadrivalent human papillomavirus (HPV) types 6/11/16/18 L! virus like particles (VLP) vaccine. *Vaccine.* 2007;25(26):4931-0.
[29] The Future II Study Group. *NEJM*. 2007; 356:1915-27.
[30] ACIP meeting October 25, 2007.
[31] Markowitz L. HPV Vaccines: Overview of Data from Clinical Trials. ACIP October 25, 2007 meeting.
[32] Research presented at the 47th Annual Interscience conference on Antimicrobial Agents and chemotherapy, Chicago, September 2007.
[33] MMWR, Quadrivalent Human Papillomavirus Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). March 23, 2007: Vol. 56 RR-2.
[34] Study presented at the 24th International Papillomavirus Conference in Beijing, China, November 2007.
[35] Centers for Disease Control and Prevention (CDC). Quadrivalent Human Papillomavirus Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR, 2007;56. RR2:16.
[36] Id.
[37] Food and Drug Administration. Product approval information-licensure action [package insert]. Gardasil (quadrivalent human papillomavirus types 6,11,16,18). Merck and Co.,Whitehouse Station NJ. Available at http://www.fda.gov/cber/review/hpvmer060806r.pdf and http://www.fda.gov/cber/label/gardasilLB.pdf; Centers for Disease Control and Prevention (CDC). Quadrivalent Human Papillomavirus Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR, 2007;56. RR2:14.
[38] Information presented at the June 28, 2007 ACIP meeting in Atlanta, Georgia.
[39] Id.
[40] Id.
[41] Centers for Disease Control and Prevention (CDC). Quadrivalent Human Papillomavirus Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR, 2007;56. RR2:14.
[42] Minnesota Statutes, Section 62A.047.
[43] Employee Retirement Income Security Act of 1974. The federal law which established legal guidelines for private pension plan administration and investment practices.
[44] This number was calculated by assuming there are 36,000 girls in one age cohort, of which 5% are underinsured or 1,800; 1,800 x $96.75/dose x 3 = $522,450. The 5% underinsured rate was taken from the 2007 Population Estimate Survey conducted by the MnVFC program.
[45] 36,000 x 58% (proportion with private insurance) = 20,880; 20,880 x $120.00/dose x 3 = $7,516,800.
[46] Saners G, Taira A. Cost-effectiveness of a potential vaccine for human papillomavirus. *Emerg. Infect Dis*. 2003;9:37-48; Goldie S, Kohli M, Grima D, Weinstein M, Wright T, Bosch F, Franco E. Projected clinical benefits and cost-effectiveness of a human papillomavirus 16/18 vaccine. *J Natl Cancer Inst.* 2004;96:604-15; Taira A, Neukermans C, Sanders G. Evaluating human papillomavirus vaccination program. *Emerg. Infect Dis*. 2004;10:1915-23; Elbasha E, Dasbach E, Insinga R. Model for assessing human papillomavirus vaccination. *Emerg. Infect Dis*. 2007;13:29-41.

Glossary of Terms

ACIP. The federal Advisory Committee on Immunization Practices. The ACIP consists of 15 experts in fields associated with immunization who have been selected by the secretary of the U. S. Department of Health and Human Services to provide advice and guidance to the secretary, the assistant secretary for health, and the Centers for Disease Control and Prevention (CDC) on the control of vaccine-preventable diseases. For more information on the ACIP go to http://www.cdc.gov/vaccines/recs/acip/.

Antibody. A protein produced by the body's immune system in response to a foreign substance (antigen). Our bodies fight off an infection by producing antibodies. Vaccines stimulate our immune system to produce antibodies in lieu of disease or infection.

Antibody titer. A measurement of the amount of antibodies in the blood. The higher the titer, the more antibody is present.

Antigen (also immunogen). A foreign substance in the body (a bacterium, virus, or protein, for example) that can cause disease — and whose presence triggers an immune response (the formation of antibodies).

Bivalent vaccine. A vaccine that contains two antigens, (e.g., Cervarix).

Cohort. A group of individuals having a statistical factor (such as age or class membership) in common in a demographic study, such as a cohort of students.

Entitlement program. A federal program that guarantees a certain level of benefits to persons or other entities who meet the requirements set by law.

Incidence. The number of new cases of a specific disease occurring during a certain period of time in the population

Morbidity. Refers to sickness.

Morbidity rate. The ratio of the incidence of sickness to the number of well persons in a given group of people over a given period of time. It may be the incidence of the number of new cases in the given time or the total number of cases of a given disease or disorder

Mortality. Refers to death.

Mortality rate. The frequency or number of deaths in ratio to population

Papillomas. Refers to a benign tumor growing exophytically (outwardly projecting) in finger-like fronds. Also referred to as warts.

Placebo. An inactive substance or treatment that looks the same as, and is given the same way as, an active drug or treatment being tested. The effects of the active drug or treatment are compared to the effects of the placebo.

Prevalence of disease. The number of cases of a disease that are present in a population at a specified time, either at a point in time or over a period of time.

Quadrivalent vaccine. A vaccine that contains four antigens (e.g,, Gardasil).

Titers. A titer is a measurement of the amount or concentration of a substance in a solution. It usually refers to the amount of medicine or antibodies found in a patient's blood.

Attachments

Attachment A

Human Papillomavirus (HPV)
Minnesota Health Care Programs
PERFORMANCE IMPROVEMENT PROJECT PROPOSAL
2007

Executive Summary

Study Topic: The focus of this Performance Improvement Project (PIP) is the promotion of Human Papillomavirus (HPV) vaccination to prevent cervical cancer in the Minnesota Health Care Programs (MHCP) population enrolled in the nine participating health plans and County Based Purchasing Organizations (the Collaborative).

Study Question:
Will promoting awareness of the HPV vaccination through member education as well as provider and key organization partnerships increase the percentage of Minnesota Health Care Program (MHCP) females eleven to twelve years of age, who have had at least one administered dose of the HPV vaccine by an absolute 5% over the baseline measure?

Study Indicators: The study indicator is at least one administered dose of HPV vaccine in accordance with the recommendations of the Institute for Clinical Systems Improvement (ICSI) Immunization Guideline (ICSI, 2007).

Study Population: The study population consists of MHCP females 11-12 years of age as of the first day of the measurement period, who are enrolled in the last month of the measurement period (December), with no more than a two month gap in coverage.

Sampling Technique: The entire MHCP study population will be analyzed; no sampling will be necessary.

Data Collection: Claims data from all Collaborative members.

Intervention Strategies:
1. Target parents and guardians of members to promote the benefits of HPV vaccination;
2. Promote partnerships with private and public clinics, school-based clinics, and physicians to perform outreach and complete vaccinations;
3. Promote partnerships with key organizations to increase awareness of the importance of HPV vaccination in the prevention of cervical cancer.

Minnesota Department of Health

The Minnesota Vaccines for Children Program (MnVFC)

What is the MNVFC program?

The Minnesota Vaccines for Children (MnVFC) program is an enhanced version of the federally funded Vaccines for Children program. MnVFC ensures that any Minnesota child whose family cannot afford immunizations can be vaccinated.

The MnVFC program at the Minnesota Department of Health (MDH) distributes $15 million worth of vaccines annually.

Why was the program created?

Many parents cannot afford to pay for vaccines on their own. When large groups of children go without vaccines, it leaves them unprotected and vulnerable to disease and disease outbreaks can happen. This program eliminates cost as barrier to children getting their vaccines on time.

How does it work?

The program provides federally purchased vaccine for eligible children at no charge to MnVFC-enrolled public and private providers. It covers vaccines recommended and subsequently approved for the program by the federal Advisory Committee on Immunization Practices (ACIP).

Providers can charge a small administrative fee, which is set by federal law for each state, but providers cannot refuse to administer the vaccine due to a patient's inability to pay the fee. Providers screen patients for MnVFC eligibility at their clinics.

Who is eligible to participate?

Children from birth through 18 years of age who meet at least one of the following criteria:

- Medicaid eligible
- Uninsured
- American Indian or Alaska Native
- Underinsured (Note: the federal VFC program only allows these children to receive VFC vaccines at federally qualified health centers (FQHC) and rural health clinics (RHC). However, Minnesota uses other sources of funding to allow eligible children to get their vaccinations from their own medical provider.)

Is the MnVFC program the same as the federal VFC program?

Not exactly. The MnVFC program supplements the federal program with approximately $ 3.5 million of discretionary federal 317 vaccine funds to expand eligibility for who can receive vaccine.

The federal VFC program is an entitlement program.

What are 317 funds?

The state receives federal money from section 317 of the federal Public Health Act. These are discretionary federal funds that must be specifically used to support the state's immunization program including the purchase of vaccine.

These 317 funds have allowed MDH to extend vaccine coverage to ensure that cost is not a barrier to all children being immunized. This includes:

- underinsured children under 18 years of age within their medical home
- college students requiring immunizations for college entrance in a Minnesota school
- newly arriving refugees
- uninsured immigrants applying for U.S. citizenship.

This 317 federal funding has remained level for about five years, despite growing costs as new vaccines are recommended and added to the immunization schedule. As a result, MDH has had to consider narrowing the criteria for who can receive vaccines purchased using 317 dollars.

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MnVFC Program Continued – page 2

Additionally, in the future, this funding squeeze may mean that some uninsured persons may need to seek a FQHC or RHC in order to obtain certain vaccines, which is a barrier to immunizations for many, since these clinics are widely spaced geographically.

How does MnVFC interact with Medicaid and other Minnesota Health Care Programs?

- Medicaid is federally mandated to cover VFC-recommended vaccines for the Medicaid population.
- In addition, Minnesota law requires that all Minnesota Health Care Program providers who administer pediatric vaccines be enrolled in the MnVFC program. Minnesota Health Care Programs include Medical Assistance (MA), MinnesotaCare, General Assistance Medical Care (GAMC), and Prepaid Medical Assistance Programs (PMAP).
- The Department of Human Services (DHS) reimburses the MnVFC program for immunizations supplied by MnVFC for adults age 19 and older who are enrolled in a Minnesota Health Care program.

What are the benefits to parents, children, providers, and the community?

- The MnVFC program saves parents and enrolled providers expenses for vaccine because providers receive public-purchased vaccines covered under this program;
- The program eliminates or reduces vaccine cost as a barrier to vaccinating eligible children;
- The program enables eligible children to receive immunizations in their medical home as part of their comprehensive health care rather than requiring them to seek immunizations from specified public clinics;
- The program makes it more likely that providers don't miss opportunities to vaccinate, so children are more likely to be fully immunized on time;
- MnVFC provides technical assistance to clinics to help improve their vaccination rates and overall immunization practices.

Additional goals of the program

While the primary goal of the program is to prevent disease by increasing immunization coverage in Minnesotans, it also focuses on safeguarding the viability of vaccines, which are very temperature and time sensitive. Therefore, a secondary goal of ensuring appropriate storage and handling will:

- ensure the efficacy of vaccines administered to patients, and
- prevent loss of valuable VFC vaccines through spoilage.

Who can I contact for more information?

For more information about immunizations in Minnesota, contact MDH's Immunization Program at 651-201-5503, toll-free 1-800-657-3970, or visit the web site at www.health.state.mn.us/immunize.

Minnesota Department of Health

Human Papillomavirus Vaccine: What You Should Know

What is human papillomavirus (HPV)?

Human papillomavirus is a common virus that infects the skin, particularly the genital area. There are over 100 types of HPV and about 40 of them are spread through sexual contact. HPV types can be broadly grouped into two categories, those that might lead to cancer and those that do not lead to cancer.

How common is HPV in the United States?

HPV infections are very common. Right now about 20 million people in the U.S. have HPV and over 6 million more are newly infected each year – mostly people in their late teens and early 20s. Many people get infected with more than one type of HPV.

What are the symptoms?

Most of the time there are no symptoms and most HPV infections go away on their own.

Some HPV types will cause an ongoing (chronic) infection in the cervix of a woman. This causes abnormal Pap smears. Chronic HPV infection can lead to cervical cancer. The only way to know if you have a chronic infection is by having regular Pap smears. HPV can also cause other types of cancer including cancer of the penis, vulva, or anus.

Other types of HPV causes genital warts, which can be uncomfortable and irritating and can reoccur but do not cause cervical cancer. Genital warts can infect a baby's lungs and airway during birth.

How common is cervical cancer?

Annual Pap smears have been highly successful in reducing cervical cancer in the United States. However, about 12,000 cases of cervical cancer occur as the result of chronic HPV infection, and about 3,700 women die of cervical cancer in the U.S. each year. In Minnesota, about 175 women are diagnosed with this disease each year and about 45 die.

How do you prevent HPV infections?

Not having sex is the surest way to prevent HPV infections. Reducing the number of sexual partners and using condoms will reduce the risk of getting an HPV infection, but may not entirely prevent infection.

There is an HPV vaccine that protects against the HPV types that cause about 70 percent of cervical cancer and about 90 percent of genital warts. The HPV vaccine will prevent HPV infection for two types of HPV that might lead to cancer. To get this protection, you need a series of three HPV shots, given in the arm.

HPV vaccine is very good at protecting young women against the most common types of HPV that cause cervical cancer and genital warts.

Does the HPV vaccine work?

Yes, it is very good at protecting young women against the most common types of HPV that cause cervical cancer and genital warts. But the vaccine does not protect against every type of HPV, and it does not help treat a person who already has an HPV infection. Therefore,

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HPV Vaccine: What You Should Know – page 2

women and girls who get vaccinated are still at risk for genital warts and cervical cancer.

With the vaccine are Pap smears still necessary?

Yes. It is still extremely important for all women to get regular Pap smears – even after they get an HPV vaccination. Pap smears save lives. The vaccine only protects against two types of HPV that cause cancer. Pap smears detect infections from other HPV types.

Is HPV vaccine safe?

The vaccine was tested in thousands of women and serious reactions were very rare. The most common complaint was that the vaccine stings. Some women also had soreness and swelling in the arm where the shot was given.

Who should get the HPV vaccine?

Young girls should get HPV vaccine as part of their preteen healthcare visit at age 11-12 years. The vaccine provides the best protection if given before a woman is sexually active. The vaccine can be given as young as 9 years old. The ACIP also recommends the vaccine for females ages 13 through 26 years who haven't yet been vaccinated.

Scientists are still studying whether the vaccine works in males and making sure that it is safe to give to them.

Can I get free or low cost HPV shots?

Yes, if you don't have insurance or your insurance does not cover the cost of HPV vaccination, you may be able to find free or low cost HPV shots.

- Talk to your private healthcare provider. If the person in need of vaccination is 18 years old or younger, they may be eligible for the Minnesota Vaccines for Children program. This program covers the cost of vaccination; however, the parent may have to pay an administration fee of up to $14.69 per shot.
- Call Merck, the company that makes HPV vaccine. If the person who needs vaccination is 19-26 years old, Merck has a program to help cover the costs. Call them at 1-800-261-5579 or go to their website at www.merckvaccines.com and click on Adult Immunization Program.
- Talk to your city or county health department. They may be able to provide low cost HPV shots.

Where can I find more information about HPV?

- Minnesota Department of Health: www.health.state.mn.us/immunize (click on Diseases Prevented by Vaccines in the left column, then on HPV)
- Centers for Disease Control and Prevention (CDC): www.cdc.gov/vaccines/vpd-vac/default.htm and click on Human Papillomavirus
- Immunization Action Coalition: www.immunize.org/HPV/
- Vaccine Education Center at the Children's Hospital of Philadelphia: vaccine.chop.edu