Cost Analysis and Modeling of HPV Vaccination

Evan R. Myers, MD, MPH

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Summary

There are multiple types of human papillomavirus (HPV) that are the primary cause of cervical, anal, and oropharyngeal cancer, thus the human and economic burden of HPV infection is significant. One vaccine against HPV infection is currently FDA approved and another is on the horizon. With vaccination, reductions in the burden of HPV related disease would be seen within five years even in women who are already sexually active. Vaccination is likely to be cost effective from the societal perspective. Overall, the most cost-effective way to reduce the HPV burden is to combine vaccination and screening beginning at a later age and at a less frequent interval than currently recommended.

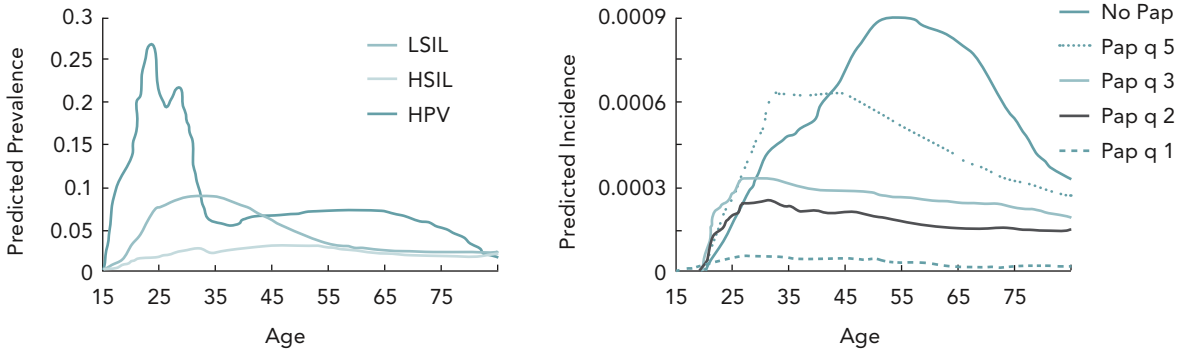
Key Points

- HPV infection is a primary cause of cervical, anal, and oropharyngeal cancer, and results in a significant number of deaths each year.
- HPV vaccines are effective at reducing disease and are likely cost-effective from a societal perspective.
- Reductions in the burden of the disease with vaccination should be seen within five years, even in unselected sexually active women.
- There are no published data on vaccination cost-effectiveness from a managed care plan perspective.
- Efficiency of cervical cancer screening is highly dependent on age of screening, on sensitivity and specificity of screening, and on frequency of screening.
- With widespread HPV vaccination, the biggest potential impact on both health and economic outcomes likely will be extending PAP screening intervals and beginning screening at a later age.

THERE ARE MULTIPLE HUMAN PAPILLOMAVIRUS (HPV) types. Four of these, which are the primary cause of cancer related to HPV, are targeted by the currently available vaccine (Gardasil®) and a vaccine that is on the horizon (Cervarix®). HPV 16 and 18, which are covered by Gardasil® and Cervarix®, are a primary cause of cervical, anal, and oropharyngeal cancer. There are other HPV types that are carcinogenic but 16 and 18 were picked because they cause about 70 percent of cervical cancers worldwide. HPV 6 and 11, covered only by Gardasil®, cause 90 percent of the cases of genital warts. Six and 11 also are the sole cause of juvenile onset recurrent respiratory papillomatosis (RRP), which is the presence of warts on the larynx. This is a chronic recurrent disease that causes significant morbidity.

One hundred percent of cervical cancer is caused by HPV. There are about 9,700 cases annually in the United States. This number would be much higher without routine PAP smear testing. Vulvar/vaginal cancers are rare, but 30 percent to 60 percent of those are caused by HPV. About 6,000 cases of vulvar or vaginal cancer occur annually. HPV 16 and 18 cause 80 percent to 100 percent of anorectal cancer cases. Annually, there are about 2,700 cases

Exhibit 1: Cost-Effectiveness of Screening – Lessons Learned



- Most efficient age to begin screening is mid-30s.
  - Peak prevalence of HPV and LSIL is past.
  - Cervical cancer incidence just beginning to rise
    - Majority of cancers haven't occurred yet.
  - Screening not as effective for cancers in younger women

LSIL, Low-Grade Squamous Intraepithelial Lesion; HSIL, High-Grade Squamous Intraepithelial Lesion

in women, and 1,900 cases in men. The incidence of anorectal cancer in men who have sex with men is about equivalent to the incidence of cervical cancer in women without any cervical cancer screening. The histology of the junction between the anus and the rectum is very similar to the transformation zone on the cervix. HPV seems to affect these areas exactly the same way.

HPV 16 and 18 cause 40 percent to 70 percent of oropharyngeal cancer. That proportion is rising, as sexual practices that lead to oropharyngeal transmission of HPV are becoming more common and smoking rates decline. About 11,000 cases in women and 20,000 in men occur each year.

All cases of genital warts are caused by HPV. The true burden of genital warts is difficult to determine because many patients do not seek treatment and it is not a reportable disease. Women make at least 357,000 initial office visits for treatment of genital warts each year. Recurrent respiratory papillomatosis (RRP) is much less common, but it is a chronic disease that requires multiple surgical procedures.

Because HPV infection leads to cancer, there are a significant number of deaths each year related to HPV. More than 3,000 women die each year from cervical cancer. Vulvar or vaginal cancer kills 1,700 each year, anorectal cancer more than 700, and oropharyngeal, 7,400.

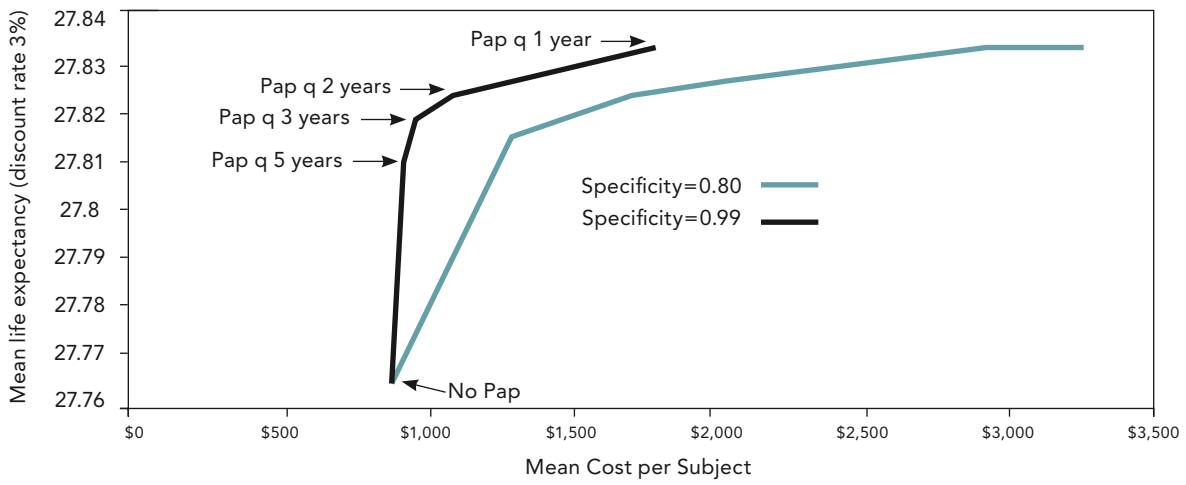
In terms of morbidity, most of the cancers caused by HPV are squamous cancers, which can usually be managed surgically, but that surgery is often disfiguring. Surgery can affect sexual, bowel, and urinary function in the anogenital area. When used for RRP, surgery can affect speech, eating, and swallowing. Radiation therapy, which also is used to treat many of these cancers, has long-term sequelae. In terms of quality of life, cancer sequelae affect multiple functions. Although many cervical cancers are curable, the treatment at the very least renders women infertile.

There is little research about the impact of HPV related disease on quality of life. Existing research does show consistent decrements. Although most abnormal PAP results will never go on to become cancer, many women have anxiety as a result of abnormal results. There also is the stigma that abnormal PAP results caused by HPV are associated with sexually transmitted diseases. Genital warts also have impact on patients in terms of stigmatization and sexual function. Recurrent respiratory papillomatosis affects speech and potentially causes airway obstruction.

The economic burden of cervical disease costs between $2 billion and $4.5 billion annually. Most of that is related to screening, diagnosis, and treatment. In the managed care arena, warts are estimated to cost $700 per thousand person-years of enrollment. Although RRP is rare, individual cases are costly. The most recent estimate is $40 million to $120 million annually.[1] HPV is second only to human immunodeficiency virus (HIV) in terms of costs among sexually transmitted diseases.[2]

Overall, HPV infection has significant impact on health and economic outcomes. Although some

Exhibit 2: Effect of Decreasing Pap Specificity at No Marginal Cost on Overall Cost-Effectiveness



HPV diseases are life threatening, the majority of the population burden is related to screening or benign disease rather than cancer.

Some important lessons have been learned from cervical cancer screening. With effective screening, there is a decreased cervical cancer incidence, detection of disease at an earlier stage, and a decrease in mortality. The incidence rate declines the most with yearly screening (Exhibit 1). In women who are not screened, about half the cases are stage 1 (confined to the cervix) at the time of diagnosis. In women who are screened, 85 percent to 90 percent of the cases are stage 1 at the time of diagnosis.

With any type of cancer screening, there is a shift of the peak incidence to younger ages because screening detects asymptomatic, early disease. The other interesting lesson, which is a key point with vaccines, is that increasing the screening coverage or the frequency has less of a benefit in younger women than it does in women in their middle years or older years. This is because of length bias – screening preferentially detects slower-growing cancers. In fact, cervical cancer is probably the ideal cancer for screening. The average length of time from HPV infection to cancer is somewhere between 15 to 20 years. Women who get HPV-related cancer at ages younger than 18 typically have cancers that are much more aggressive than average.

When looking at cost effective screening models, the most efficient age to begin cervical cancer screening is the mid 30s. This is because the peak prevalence of any HPV infection is between the ages of 15 and 35 (Exhibit 1). By screening after age 35, asymptomatic HPV infections that cause abnormal changes in the PAP smear, and require follow-up, are not detected. At 35, the prevalence of high-grade lesions, which are more likely to become cancerous, is just beginning to rise. Cervical cancers in younger women are not that amenable to prevention through screening.

Another lesson that has been learned is that the incremental cost effectiveness ratio (the cost per extra life year saved) increases dramatically as the frequency of screening increases, the sensitivity of the screening test increases, and the specificity of the screening decreases. Costs increase more than the benefits in terms of saving a life and increasing life expectancy when cervical cancer screening is more frequent (one-year versus five-year intervals). The reason is that more tests are conducted. With more frequent testing, more false positives occur. Most mild changes in the cervix caused by HPV will reverse within one to two years. Frequent screening detects those mild changes and results in additional testing.

The cost efficiency also decreases as sensitivity of the test frequency increases (Exhibit 2). This is a little bit counter-intuitive, but it is because most of the extra disease detected is not true disease in the sense that it is not going to become a cancer.

Going from no screening to screening every five years is very cost efficient. It does not save money but it is very efficient; screening tests never save money.

The lifetime incidence of any HPV infection in sexually active men and women is somewhere between 80 percent and 95 percent. Very few of those people will have cancerous changes. Better ways to identify who is really at risk for developing cancer are needed. The biggest priority for cervical cancer screening is to get women who aren't being screened or being under-screened into the system in

the first place. The majority of the failures to detect cervical cancer cases in this country are not caused by screening test failures; they are caused by women not getting screened.

One vaccine against HPV infection is currently FDA approved and another is on the way. Based on published data, these vaccines have greater than 90 percent efficacy in naïve populations (HPV negative) against vaccine covered HPV types and approximately 50 percent efficacy in unselected patients.[3] The reduced efficacy in unselected populations is because a prophylactic vaccine is not going to prevent disease or infection that already is present. There is a reduction in disease burden in unselected patients seen within three years. The relative reduction is greatest for cervical intraepithelial neoplasia [CIN] 2/3 or moderate to high-grade dysplasia, but absolute reduction is highest for CIN 1 or low-grade dysplasia, which is the most common screening abnormality.

There are some caveats to interpreting the HPV vaccine trial data. Screening was more frequent in trial protocols than typical practice. This probably overestimates the absolute reduction in disease. Additionally, some lesions detected in the trials would likely not be detected in practice. At this time, there are no data on cancer outcomes with the HPV vaccine, but this is not surprising given the age of the subjects.

The HPV vaccine is targeted at adolescent or pre-adolescent girls in order to vaccinate before exposure. When looking at HPV vaccine reduction of disease burden models, the published models estimate substantial reduction in disease burden with vaccination under a wide variety of assumptions. Vaccination at current and projected prices is cost-effective and in the range of $50,000 to $75,000 per quality-adjusted life year. Cost-effectiveness is improved if reduction in transmission is included. A large proportion of cost reductions are associated with reductions in genital warts and mild screening abnormalities that would require additional testing and follow-up.

Some of the issues with the modeling studies that have been published include very limited data on quality of life, almost no data on transmission dynamics of HPV, and difficulties in adequately modeling HPV as a sexually transmitted disease. Additionally, there are no data on duration of vaccine efficacy beyond five years. A booster vaccination is likely to be cost-effective if needed to extend protection to age 30. Extending protection beyond that probably is not cost-effective because the incidence is lower. It also is difficult to include genital warts in the cost-effectiveness models because of lack of data.

In the first five years after vaccination, 97 percent of the disease reduction is with the 6 and 11 types, and that continues to be a large part of disease reduction over time.[4] Inclusion of HPV 6 and 11 in one vaccine is likely to have short-term benefits. In the short term, most of the cost reduction is due to reduction in benign lesions (HPV 6 and 11). As more and more cervical cancers are prevented, the proportion of the costs avoided attributable to HPV 16 and 18 increases with time. Currently, there are no published data on cost-effectiveness from a managed care plan perspective.

In addition to the possible need for booster vaccination, one issue with HPV vaccination includes whether there is an upper age limit for vaccination. There are ongoing trials using Gardasil® in women aged 25-45. In the Future III

Exhibit 3: Effect of Vaccine on Negative Predictive Value of Biennial Screening, Beginning Age 18

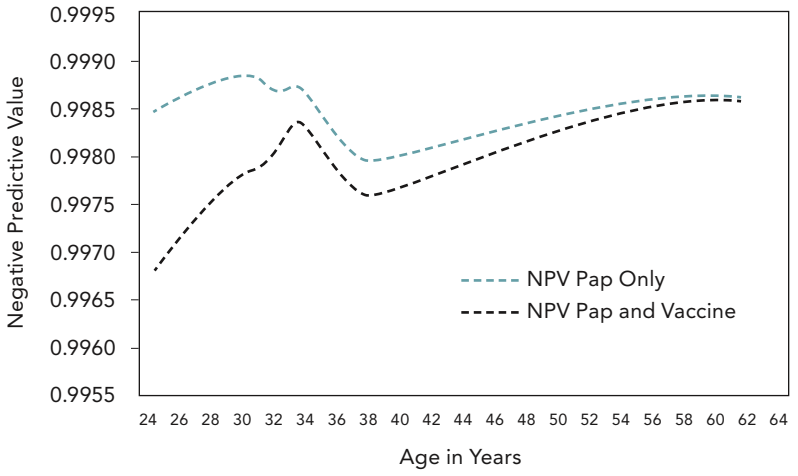
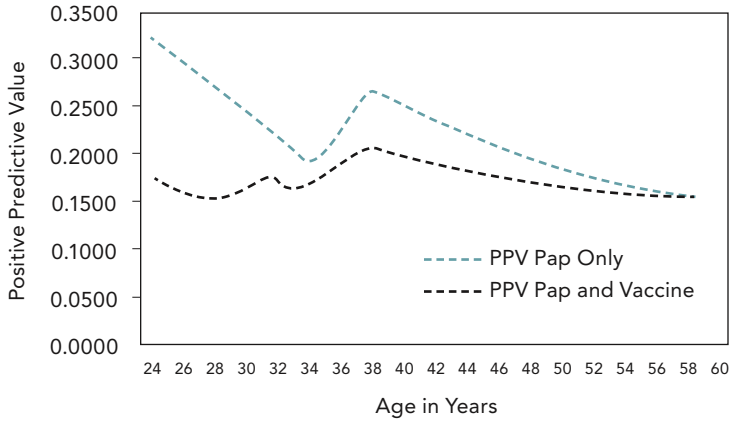


Exhibit 4: Effect of Vaccine on Positive Predictive Value of Biennial Screening, Beginning Age 18



trial, the overall efficacy in 3,800 women aged 24 to 45 was 96 percent. Since males transmit the disease to women and suffer from HPV-related diseases, people have questioned whether boys also should be vaccinated. Trials also are ongoing to address this issue. In theory, vaccinating 50 percent of boys and 50 percent of girls should be the same as vaccinating 100 percent of girls. Vaccinating boys will provide some protection against oropharyngeal and anal cancers, as well as protection against genital warts. The immunogenicity data also suggest that the immune response in boys is greater than it is in girls.

In women who have been vaccinated against HPV, the positive predicted value of a PAP test will be lower and the negative predictive value will be higher. This is because the predictive value of the test is dependent on the specificity and the prevalence of the disease. Prevalence of cervical changes will be decreased by vaccination. Thus, there will be more false positives. Because the negative predicted value will be higher, there is additional safety in extending the intervals between PAP tests.

Overall, the most affordable way to combine vaccination and screening would be to extend the screening intervals and begin screening at a later age. Screening is very inefficient in younger women; it has a high degree of false positives and the treatments may have a lot of morbidity. Modeling suggests equivalent cancer incidence and lower costs for combining HPV vaccination with biennial PAP screening starting at age 24 versus annual screening beginning at age 18.

Exhibits 3 and 4 show how the negative and positive predictive value of a PAP test changes over time with vaccination. The negative predicted value goes higher as the cohort ages because cancer is being detected, and the incidence of cancer becomes lower. The positive predicted value goes down with age, with PAP only, but it starts at a low value in women who have been vaccinated. HPV vaccination intensifies the need for more specific cervical cancer screening tests. Better prediction of who is truly at risk will be needed in a vaccinated cohort.

Conclusion

With vaccination, reductions in the burden of HPV related disease will be seen within five years, even in women who are already sexually active. Vaccination is likely to be cost effective from the societal perspective. Inclusion of HPV types 6 and 11 is likely to have short-term benefits as well as some cost efficiencies. Screening policies need to change to provide the most cost effective combination of vaccination and screening. **JMCM**

Evan R. Myers, MD, MPH, is chief of the Division of Clinical and Epidemiological Research for the Department of Obstetrics and Gynecology at Duke Clinical Research Institute and senior fellow at the Center for Clinical Health Policy Research.

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