Challenges in Vaccine Policy:
A Case Study of the HPV Vaccine

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Preface

This report is the fifth in the *Innovation Series* published by the New England Healthcare Institute (NEHI). The goal of this series is to identify opportunities to accelerate the adoption of highly valuable innovations that will benefit patients and help contain U.S. health care costs. Focusing on emerging innovations for the treatment of major diseases, such as cancer, cardiovascular disease, and diabetes, these reports analyze specific classes of innovation, identifying the size and nature of their impact, their importance, value, drivers, and barriers to adoption. Each report closes with recommendations for actions that major stakeholders (e.g., manufacturers, regulatory agencies, payers, patients, clinicians) can take to help speed an innovation's journey from initial concept to accepted clinical practice. NEHI draws upon its industry-wide membership to guide the development of these recommended actions.

Previous NEHI *Innovation Series* Reports:

Targeting Cancer: Innovation in the Treatment of Chronic Myelogenous Leukemia (March 2004)

Remote Physiological Monitoring: Innovation in the Management of Heart Failure (July 2004)

Continuous Glucose Monitoring: Innovation in the Management of Diabetes (March 2005)

Insulin Analogs: Innovation in Biotechnology (January 2006)

Executive Summary

OVERVIEW

Despite a history of remarkable successes and recent advances in research and development, today's U.S. vaccine enterprise is strained. Recent years have seen supply shortages, insufficient public and private funding, suboptimal immunization rates, disparities in access, and a decline in the public's appreciation of the value of vaccines.

The HPV vaccine presents a unique opportunity to fix what is broken throughout the broader immunization system.

Against this backdrop, the new human papillomavirus (HPV) vaccine is emerging, with the promise of greatly reducing cervical cancer in women. But, unless there are improvements, these same system-wide challenges will keep this important breakthrough from realizing its full potential.

On the other hand, since so many of the issues are the same, repairing the road that leads to maximum adoption of the HPV vaccine presents a unique opportunity to fix what is broken throughout the broader immunization system.

This report provides an in-depth study of the HPV vaccine for the prevention of cervical cancer. Our analysis includes an overview of the vaccine's promise and value to patients, a discussion of the barriers that could impede its timely adoption, and a detailed call to action that – if acted upon – will systematically strengthen the adoption of all vaccines.

VACCINES' PAST SUCCESSES AND FUTURE PROMISE

Vaccines are one of the most successful public health tools in history. During the 20th century alone, vaccines have dramatically reduced or eliminated morbidity from a number of diseases common in the United States, such as smallpox, diphtheria, and polio.[1]

Vaccines are more critical today than ever in the face of such emerging threats as global pandemics, bioterrorism, and new diseases like SARS and HIV.

In recent years we have seen a number of new vaccines that target a range of diseases such as meningococcal meningitis, herpes zoster, rotavirus and, most recently, the human papillomavirus, which is known to cause cervical cancer. Successful adoption of these vaccines will improve the public's health.

VACCINE ENTERPRISE UNDER STRAIN

Notwithstanding these notable advances, the U.S. vaccine enterprise is strained. Its problems begin upstream, where research and development costs have risen in an economic environment that has squeezed prices and thus diminished revenues. Moreover, clinical trials and manufacturing requirements have tightened. There are wide gaps in public and private funding for vaccine coverage, so that some children, as well as many adolescents and adults, lack access. At the same time,

insufficient reimbursement limits the attention and time clinicians devote to immunization.

Systemic problems include poor record keeping, insufficient infrastructure and delivery mechanisms, and a lack of emphasis on prevention and immunization for adolescents and adults. Most adolescents and adults are uninformed about the vaccines they should be getting, much less where and when to get them.

Finally, in recent decades, public appreciation of vaccines has waned – we no longer fear the very diseases that vaccines prevent. In addition, despite the fact that vaccines have had an exemplary safety record, a number of anti-vaccine groups have formed and have had a disproportionate, dampening effect on the public's perception of vaccines and on overall demand.

All of these challenges have resulted in a broken system that undervalues vaccines, limits patient access – especially for adolescents and adults – and, at worst, threatens our public health.

THE HPV VACCINE: INNOVATION IN THE PREVENTION OF CERVICAL CANCER

The emerging HPV vaccine has the potential to greatly reduce cervical cancer for millions of women in the U.S. and worldwide. But it faces many of the same barriers that stand in the way of other vaccines. Hence, fixing what is broken for the HPV vaccine could, in turn, repair many of the challenges facing all vaccines.

The Burden of HPV and Cervical Cancer: a Complex, Costly Disease

There are approximately 6.2 million new HPV infections each year, and about 20 million men and women have HPV at any given time.[2,3,4] The virus is so prevalent that an estimated three in every four Americans aged 15 to 49 will become infected with HPV at some point in their lifetime.[5] Direct annual medical costs of treating symptoms of HPV in the U.S. are estimated to be $1.6 billion.[6]

Of the many strains of HPV, 16 and 18 are the most carcinogenic and most prevalent; subtype 16 causes over half of all cervical cancers, worldwide.[4,7] And despite well-organized screening programs in the U.S., there are an estimated 9,700 new cases of cervical cancer each year, resulting in over 3,700 deaths.[2]

Screening and Treatment Are Effective…But Not Foolproof

Due to relatively high screening rates, cases of cervical cancer in the U.S. plummeted by 74 percent between the introduction of the Pap test in 1955 and 1992.[8] Nevertheless, cervical cancer screening has its own limitations, related to accuracy, follow-up, and patient access. Furthermore, screening is not as accessible to low-income, immigrant, rural, and minority women who suffer disproportionately high rates of cancer as a result. Overall screening rates in the U.S. are falling.

Emergence of the HPV Vaccine

Today, there are two products within this class of vaccines and both show immense promise in preventing cervical cancer. Merck & Co.'s quadrivalent

vaccine, Gardasil®, protects against the subtypes 16 and 18, as well as 6 and 11, the latter two of which cause 90 percent of genital warts. GlaxoSmithKline, Inc. (GSK) has developed a bivalent vaccine Cervarix®, which protects against two HPV subtypes: 16 and 18. The former recently received FDA approval, and GSK plans to submit its product for FDA approval by year-end.

High Value Potential

Results from large Phase II clinical trials demonstrated that the quadrivalent vaccine was 86-89 percent effective and the bivalent vaccine 100 percent effective in preventing persistent infection with HPV subtypes 16 and 18.[9,10] Both vaccines were nearly 100 percent effective in preventing precancerous lesions.[11]

Four independent cost-effectiveness studies on the HPV vaccine have been published.[12,13,14,15] When compared to current cervical cancer prevention protocols, all of these studies found that a prophylactic vaccine targeting high-risk HPV subtypes decreased cervical cancer risk by 46 to 66 percent and significantly increased quality-adjusted life expectancy with a cost-effectiveness ratio ranging from $14,600 to $24,300/QALY. The bottom line from all these studies is that the HPV vaccine is cost-effective.

Additionally, the true value of the HPV vaccine is likely to be even higher. These studies do not factor in additional benefits that the HPV vaccine may provide: a decrease in other HPV 16 and 18-related cancers, the avoidance of psycho-social impacts of contracting an HPV-related condition, and the protection offered to non-immunized individuals through herd immunity.

Momentum Is Building

Many stakeholders have already embraced the HPV vaccine and are actively engaged in driving its adoption through campaigns to promote public awareness. Professional societies, local governments, and organizations that advocate for women and minorities are also beginning to organize and develop plans to promote the adoption of the HPV vaccine.

Even groups that had moral objections to the vaccine have come out with messages of support, as long as the vaccine is not mandatory. Initial market research also indicates that clinicians, parents, and young adults would likely accept the vaccine if it were available. Lastly, the vaccine's approval by regulatory and recommending bodies is a strong catalyst for adoption by clinicians, professional societies, and public and private funding programs.

SIGNIFICANT BARRIERS IMPEDE ADOPTION

Our research indicates that overcoming barriers to financing, delivery, and public acceptance will help ensure successful HPV immunization, nationwide.

Public Financing Gaps for Adolescents and Adults

Today, a patchwork of private and public funding limits access to vaccines and creates disparities in a market where compliance is dependent upon adequate

coverage. There are still some gaps in funding for children and adolescents, while public financing for adults is almost nonexistent.

Although most health insurance plans provide some coverage for immunization if it is strongly recommended by the Advisory Committee on Immunization Practices (ACIP) and professional societies, some private plans do not cover adult and adolescent vaccines, and those that do may require patient cost-sharing. As many as 10-30 percent of adolescents and adults with private insurance are not covered for vaccines.[16]

Inadequate Delivery System Hinders Mass Immunization

Other primary challenges for adolescent and adult immunization include:

Infrequent prevention visits – Adolescents and young adults are a challenging group to immunize, since many do not receive regular preventive care and clinicians miss opportunities to immunize at sick visits. Recent data suggest that just over half of females ages 11 and 12 - an important target population for the HPV vaccine - have an annual preventive health visit.[17]

Inadequate data tracking – Our system does not adequately track adolescent and young adult immunizations at both the individual and population level. As a result, it is difficult for clinicians to accurately assess a patient's immunization status and for public health officials to monitor the progress of immunization programs. Important tracking tools, such as immunization registries, are not widely adopted – only 39 percent of all private clinicians submit data for childhood immunizations.

Insufficient reimbursement for clinicians – Clinicians report that reimbursement for immunization is simply inadequate to cover the cost of purchasing, storing, and administering vaccines.[18] Moreover, without proper tracking tools, it is difficult for clinicians to determine patient insurance eligibility, complicating paperwork.

Regimen and Uninformed Public Are Barriers to Public Acceptance

Today's health care delivery infrastructure is not built to accommodate the administration of three shots to an adolescent or young adult patient in the six-month interval required for the HPV vaccine. Compared to children, adolescents make few preventive health visits, and they have no established structure or routine for immunizations. Just the travel time, out-of-pocket costs, and consent laws that are associated with the HPV vaccine regimen are likely to make adoption problematic.

Patients and their parents have little knowledge about HPV and its risks, such as how one contracts HPV, the various types of virus and what they do to the body, the link to cervical cancer, or the need for early immunization.

Finally, clinicians might be resistant to discussing the HPV vaccine and sexual health issues with parents and young adolescents.

A CALL TO ACTION FOR THE HPV VACCINE AND FUTURE VACCINES

It seems clear that there is a lot to be gained by galvanizing all the stakeholders in the U.S. vaccination system to overcome the barriers that remain for mass HPV immunization, thereby strengthening the progress of *all* immunization programs in this country. To achieve the best outcome, we recommend the following steps be taken as soon as possible:

Harness public support through both wide-scale and targeted education campaigns.

A well-informed and impassioned public can drive increases and expansions in financing vaccines, plus improve vaccine acceptance and adoption. To achieve this, we need a general education campaign focused on the value and importance of vaccines to our public health, and a targeted campaign aimed specifically at driving the adoption of the HPV vaccine.

For a broad education campaign to be successful, we recommend that the National Immunization Program (NIP), a division of the U.S. Centers for Disease Control and Prevention, take the lead. We also recommend that the NIP create a coalition of supporters with aligned interests. These include state health departments, vaccine advocacy groups, public health organizations, vaccine manufacturers, and others. We also urge pooling the group's resources to engage a qualified public relations firm that can design and launch a unified, high-profile campaign, focused on the importance of vaccines to our public health, the responsibility of each individual to obtain all recommended vaccines, and the need for greater public financing.

For the targeted campaign, groups focused on cancer prevention, sexual health, health disparities, global health, and women's health should all work closely with one another – and with manufacturers – in order to maximize resources. Together, they should develop consistent messages targeted at adolescent females, their parents, and young women to inform and educate them about the HPV vaccine. To help reduce health disparities, stakeholders must ensure that such materials are culturally and linguistically accessible to a wide range of ethnic and racial minorities.

Strengthen the vaccine delivery system within our current health care system by…

Institutionalizing immunization visits for adolescents and young adults. To institutionalize immunizations for adolescents and young adults, clinicians must put in place a health care delivery infrastructure with three preventive visits for immunization: one at ages 11-12, for initial immunization (such as HPV), and the other two at ages 14-15 and 17-18 that would be used to administer any newly recommended vaccines. Professional societies, like Society for Adolescent Medicine and adolescent health departments of major academic medical centers, should lead this effort.

Educating clinicians about the importance of vaccines for adolescents and young adults. Professional societies should quickly develop and disseminate information that includes guidance on specific diseases and vaccines, as well as how to

communicate with adolescent and young adult women about sexual health. This information can be delivered via guidelines, peer reviewed journals, websites, thought-leader endorsements, conferences, medical societies, and continuing medical education.

Leveraging technology and tools for tracking immunizations. Clinicians, state public health departments, and the CDC must renew their commitment to supporting, enhancing, and populating state vaccine registries and expanding them to include adolescents, with some kind of reminder or recall mechanism. The CDC, state public health departments, and professional societies must also work with individual clinicians to educate and encourage them to systematically input data for every patient.

Aligning appropriate incentives and support. We suggest that professional societies capitalize on Medicare's recent increases in reimbursement rates by working with clinicians and private payers to ensure the implementation of these new rates as soon as possible. Another emerging solution that will help bring clinicians on board is pay-for-performance programs that reward them for high immunization rates.

Continue to expand the delivery system to include alternative sites.

Large-scale, voluntary immunization programs for the HPV vaccine will require additional venues beyond the clinical setting. Schools, pharmacies, and urgent care sites are naturals, since they already have experience administering vaccines. Because most schools have limited resources, community health departments will need to take the lead in handling the administration and financing involved.

Moving beyond the physician's office to any of these sites makes registries and record-keeping even more important. Plus, these tools have to be geared up to track adolescent and young adult vaccinations.

Entirely new venues should also be considered for the target demographic, including shopping centers, clinics within local retailers, and community centers. Employers, faith-based organizations, and service groups can do much to educate their constituents, plus sponsor immunization drives and mobile clinics.

CONCLUSION

The HPV vaccine's immense promise in preventing cervical cancer, and the fact that it faces many of the same problems that face all vaccines today, make it an ideal vehicle for implementing important improvements in the U.S. immunization system. Unless we take up the call to action and solve these challenges in financing, delivering, and adopting vaccines, the immense benefits of this vaccine, and future vaccines, will not be realized.

Introduction

VACCINES: PAST SUCCESS AND FUTURE PROMISE

Vaccines are one of the most beneficial and cost-effective public health interventions ever created.[19,20,21] Since Edward Jenner first discovered the concept of vaccination against smallpox by inoculating individuals with cowpox, vaccines have prevented millions of illnesses and deaths per year.[19] In the United States, vaccines have drastically reduced or eliminated the morbidity associated with nine major diseases (Figure 1-1).[1]

Despite such enormous success and promising scientific advancements, the U.S. vaccine enterprise is strained.

Figure 1-1:

VACCINES DRAMATICALLY REDUCE DISEASE IN THE UNITED STATES

Disease	Baseline 20th Century Morbidity	2005 Morbidity	Percent Decrease
Tetanus	1,314	20	98.5
Poliomyelitis	16,316++	1	99.9
Haemophlius influenzae type B	20,000^^^	199	99.0
Rubella	47,745+++	16	100.0
Smallpox	48,164*	0	100.0
Diphtheria	175,885+	0	100.0
Pertussis	147,271^	21,003	85.7
Measles	503,282^^	62	100.0
Mumps	152,209***	265	99.8

Source: CDC. Percent decrease has been rounded to the nearest tenth. For further notes on statistics, please refer to endnotes.[22] 2005 data is provisional.

In addition to their health benefits, immunizations have also saved substantial public health dollars – particularly through high immunization rates for children. Experts have suggested that for each dollar spent on a vaccine, $5.80 has been saved in direct medical costs.[23]

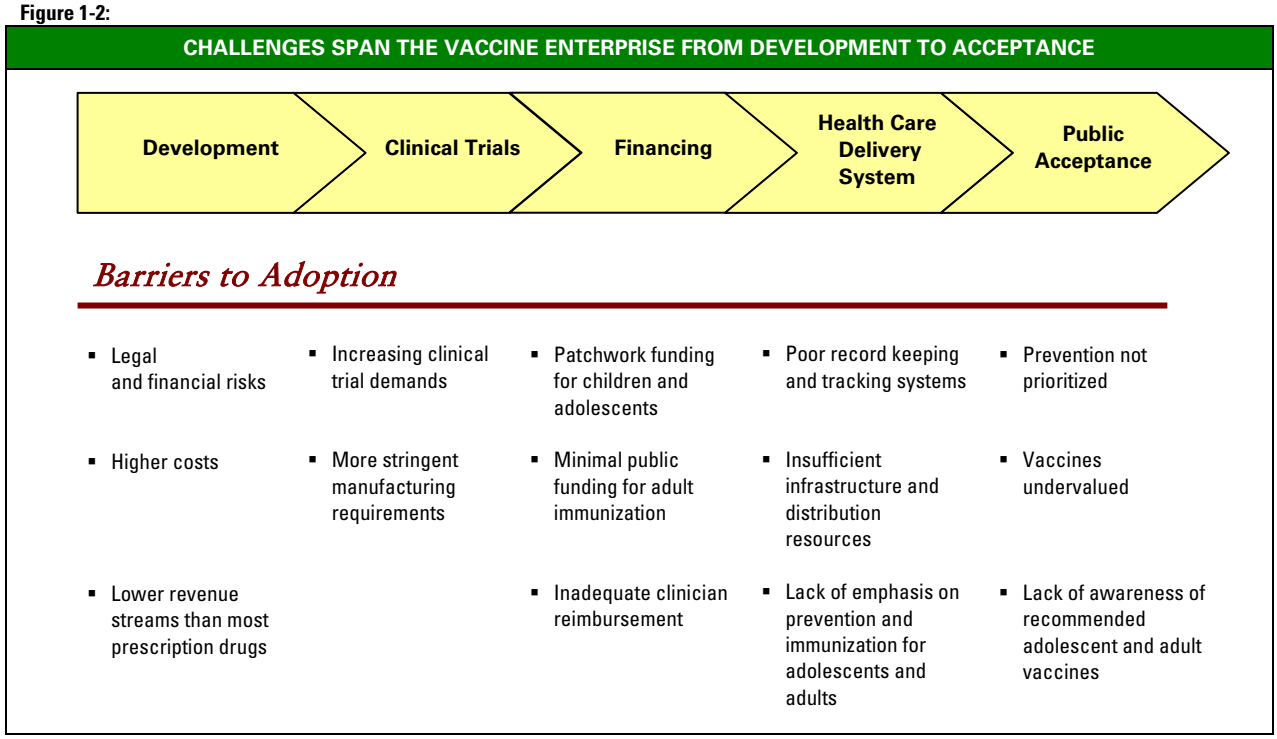
Vaccines are more relevant today than ever. With advances in science and technology, vaccines will someday allow us to combat new threats, such as HIV, bioterrorism, and pandemic flu. They also continue to fight old scourges such as malaria, cholera, and now even cancer.

Over the past few years, new vaccines that target meningococcal meningitis, herpes zoster, rotavirus, and the human papillomavirus (HPV) have hit the market. Newer vaccines have demonstrated that they can – with the appropriate support and a high adoption rate – be a lucrative investment. Prevnar® (a pneumococcal conjugate vaccine), for example, generated sales over $1.5 billion in 2005.[24] Such successes have resulted in an increase in private investment; over the past decade the pipeline for emerging vaccines has tripled to 150 today.[25]

CHALLENGES TO THE VACCINE ENTERPRISE

Despite such enormous success and promising scientific advancements, today's U.S. vaccine enterprise is strained, from development, to financing, to delivery, and acceptance. As a result, in recent years, we have seen examples of supply shortages, insufficient public and private funding, suboptimal immunization rates, increasing disparities in access, and a sharp decline in the public's appreciation of the value of vaccines (Figure 1-2). Because these problems stem from issues that are deeply rooted in our current system, they challenge the sustainability of vaccines, both now and in the future, and pose a substantial threat to public health.

Figure 1-2:



Source: NEHI

Increasing Development and Clinical Trial Demands

Over the past three decades, declining financial incentives, a higher degree of technical complexity, increasing costs of producing safe and effective vaccines, and consolidation have reduced the number of large companies engaged in the development of vaccines from 25 to five.

Increasing liability risks, as well as more complex development, manufacturing and regulatory processes, have driven R&D costs up, while the government's purchasing power and other reimbursement issues have put downward pressure on pricing.[26] Moreover, when compared to the recurring revenue streams of most pharmaceuticals, vaccines traditionally have had far less sales potential. All told,

these forces have reduced incentives for companies to continue investing in the development of vaccines, as opposed to alternatives.

Fortunately, there has been a resurgence of interest in vaccines over the past few years, apparently driven by both the introduction of new vaccines with greater revenue potential, like Prevnar®, and decreasing concern over the pricing of older vaccines.[27] Nevertheless, challenges regarding development, manufacturing, and regulatory processes persist.[25]

Insufficient Financing

Patchwork funding for vaccines, consisting of federal, state, and local funds as well as private payer funding, has resulted in gaps in coverage, especially for adolescents and adults. These gaps, in turn, have caused disparities in patient access to life-saving vaccines and suboptimal immunization rates.[16] Financing for adults is especially problematic. In contrast to funding for childhood immunization, few public dollars are being allocated to meet the needs of adults who cannot afford immunization.[28]

Moreover, evidence suggests that insufficient reimbursement for immunization puts pressure on clinicians, limiting the time spent and priority placed on doing in-office immunizations, or, at worst, the ability to offer them to their patients at all. These financing challenges not only threaten our ability to provide equal access to vaccines, they cause lower than ideal immunization rates, which can jeopardize the additional benefits vaccines provide through herd immunity.[i]

Inadequate Delivery System

Our current system for immunizing adolescents and adults is inadequate. Insufficient investment in prevention and wellness has resulted in limited preventive health care visits. This, in turn, limits opportunities for clinicians to immunize these populations. Furthermore, poor immunization records and the lack of effective tracking systems make it difficult for many clinicians to assess immunization status and generate reminders. And, since the potential of non-traditional immunization venues has yet to be fully exploited, there are few, if any alternatives. It follows that without the appropriate structures and tools in place, we will not achieve the important goal of wide-spread immunization across our adolescent and adult populations.

Waning Public Acceptance

The U.S. population has long failed to make prevention a priority, and immunizations are no exception.[29,30] While the public is aware of the need for childhood immunizations, many are less familiar with the recommendations for adolescent and adult vaccines. Others are misinformed about their risks of disease and choose to forgo immunization, especially if they are required to pay out-of-pocket.

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[i] Herd immunity refers to the protection against a disease that a non-immunized person obtains when the vast majority of the population is immunized, making transmission unlikely.

Moreover, over the years, a growing number of anti-vaccine groups have formed, concerned over vaccine safety. Despite efforts by regulatory agencies, policy makers, and manufacturers to respond to these concerns, and despite the fact that vaccines have had an exemplary safety record, the anti-vaccination movement's "zero-risk" mentality has had a disproportionate, dampening effect on vaccine demand, and consequently on development.[19]

Additional Challenges Ahead

The combined impact of all these challenges has resulted in a broken system that undervalues vaccines, limits patient access – especially for adolescents and adults – and, at worst, threatens everyone's health. Unfortunately, most of these challenges are not getting any easier as new and emerging vaccines are expected to place further pressure on a system that is already squeezed.

Due to the increasing complexity of diseases being addressed, increasing regulatory expectations, and increasing production costs, newer vaccines are likely to be more expensive than in the past, only exacerbating the financing crunch. In addition, many emerging vaccines target adolescents and adults, yet, as noted, our infrastructure for immunizing these populations is vastly inadequate. The fact that many new vaccines are targeting sexually transmitted infections only adds another layer of complexity to these problems (Figure 1-3). For one thing, it has brought cultural and religious sensitivities into play, which may create additional barriers to public acceptance.

Figure 1-3:

VACCINES IN THE PIPELINE FOR ADOLESCENTS AND YOUNG ADULTS

Sexually Transmitted Infection Vaccines	Prophylactic Cancer Vaccines	Other Vaccines[34]

• Herpes simplex virus 2 (HSV2)
• Chlamydia
• Gonorrhea
• HIV
	• Hepatitis C
	• Epstein-Barr Virus
	  ◦ Lymphoma
	  ◦ Stomach Cancer[31]
	
	Therapeutic Cancer Vaccines*
	
	• Melanoma[32]
	• Breast Cancer[33]
		• Cytomegalovirus (CMV)
		• Respiratory syncytial virus
		• Group B streptococcus

Source: IOM. *Note: Therapeutic cancer vaccines are intended to treat, not prevent, cancer, and may be seen differently by health care community than traditional vaccines. It is expected that the vaccines listed under "other" will be given to adolescent females with the goal of protecting their fetus if and when they become pregnant.

Lastly, as the above chart indicates, several new vaccines target cancer prevention. This brings new stakeholders to the table, such as cancer patient advocates and OB/GYNs, who also require education and information about immunizations.

If the U.S. is to ensure equal access to life saving immunizations in the coming years, stakeholders must work to address both long-standing *and* emerging

challenges of our vaccine enterprise. With one type of HPV vaccine FDA-approved in June 2006 and the second slated to be submitted for approval by the end of the year, the time to act is now.

THE HPV VACCINE: A CALL TO ACTION

The new human papillomavirus (HPV) vaccine holds great promise to significantly reduce cervical cancer, a disease caused by the sexually transmitted infection, HPV.[ii] Despite its potential, this vaccine faces the same long-standing challenges that vaccines have faced for years. In addition, because it targets teens and young adults who are being immunized against a sexually transmitted infection, it has an even steeper hill to climb.

But most of the barriers that stand in the way of HPV immunization are emblematic of the challenges faced by today's U.S. immunization enterprise. And, fortunately, this very convergence presents a unique opportunity by sounding a call to action to fix what is broken in the entire system. Our research indicates that a concerted effort to address the many barriers that stand in the way of HPV immunization will not only help ensure its widespread use across all strata of our society, but will also improve the outlook for *all* effective vaccines, thereby improving the health and the quality of life for millions of Americans for generations to come.

[ii] NEHI's report refers to a class of innovation; the term "HPV vaccine" refers to a prophylactic vaccine against high-risk HPV subtypes; it does not refer to any specific manufacturer's product.

The HPV Vaccine: Innovation in Cervical Cancer Prevention

To understand the full potential value of the HPV vaccine and the importance of improving its chances for optimal adoption, it is necessary to consider:

- The burden that HPV places on U.S. society.
- The ability of the HPV vaccine to mitigate this burden.
- The assessments of the vaccine's value and cost-effectiveness.

THE BURDEN OF HPV AND CERVICAL CANCER: A COMPLEX, COSTLY DISEASE

As the primary cause of cervical cancer, the human and financial burden of HPV is staggering.

Until the launch of mass market advertising in 2006, there had been scant public awareness about genital HPV, let alone its proven connection to cancer. This is despite the fact that it is the most common sexually transmitted infection (STI) in the U.S.[iii] There are approximately 6.2 million new HPV infections each year, and about 20 million men and women have HPV at any given time.[2,3,4] The virus is so prevalent that an estimated three in every four Americans aged 15 to 49 will become infected with HPV at some point in their lifetime.[5]

While many forms of the virus are harmless, certain strains can be deadly. There are over 100 types of HPV, a family of small, non-enveloped, circular double-stranded DNA viruses that can cause abnormal cell growth. Over 30 of these types are spread through sexual contact. Unlike other STIs that are transmitted via bodily fluids, HPV is sexually transmitted via skin-to-skin contact.

Some strains of HPV are considered "high-risk", (e.g., HPV 16, 18, 31, and 45), because research has shown that persistent infection with these types may lead to cancer of the cervix and other types of cancer.[35,36] Of these, HPV 16 and 18 are the most carcinogenic and most prevalent; subtype 16 causes over half of all cervical cancers worldwide.[4,7] Other strains are considered "low-risk" (HPV 6, 11, 42, 43, and 44), since they may cause mild Pap test abnormalities or genital warts, but typically do not cause cancer.[37]

As the primary cause of cervical cancer, the human and financial burden of HPV is staggering. Despite well-organized screening programs in the U.S., there are an estimated 9,700 new cases of cervical cancer each year, resulting in over 3,700 deaths.[2] Worldwide, especially in areas lacking adequate screening programs,

[iii] There are many forms of HPV, some are sexually transmitted, others are found on hands, feet, and in the throat. The vaccines discussed in this report target HPV that is sexually transmitted.

cervical cancer is the second most common cancer in women, killing over 288,000 women a year.[38]

To add to these challenges, screening for and treating HPV in the U.S. is extremely costly, incurring the highest direct medical costs of all STIs, other than HIV.[39] The cost of the cervical cancer screening program alone is $5-6 billion annually.[40] Direct annual medical costs for treating symptoms of HPV infection in the U.S. are estimated to be $1.6 billion.[40,41]

The personal toll of HPV is substantial, and not just in terms of quality of life. First, diagnosis of HPV often causes patients feelings of anxiety, stress, and fear of stigma.[42] In addition, the treatments for cervical abnormalities from HPV are invasive, painful, impact fertility, and require frequent follow-up.

Treatment for cervical cancer is also grueling, often consisting of surgery and radiation therapy. Radiation itself is yet another step that can render a woman infertile, and it can also result in severe side effects, such as diarrhea, nausea, and long-term sexual, bowel, and bladder problems.[43] Surgery may also lead to infertility and to temporary or permanent sexual dysfunction, which then often leads to depression.[44]

SCREENING AND TREATMENT ARE EFFECTIVE...

Today, there is no cure for HPV. But cervical cancer *can* be prevented or delayed through appropriate screening and treatment. The most effective screening tool is a Pap test which involves a clinician taking a sample of cells from the cervix to detect cellular changes that signal the presence of HPV. Typically, if a Pap test comes back abnormal, follow-up is recommended.

While most HPV infections clear on their own, if cervical abnormalities persist a colposcopy and/or biopsy will be performed, sometimes with an HPV test that can identify 13 of the high-risk HPV types associated with the development of cervical cancer.[45] If a pre-cancerous lesion or cervical cancer is detected, further treatment will be started. Treatment options, depending on the abnormality identified, include removal of the abnormal tissue by loop electrode excision procedure, laser surgery, conization, cryosurgery, or hysterectomy. A diagnosis of cancer may require subsequent radiation therapy and/or chemotherapy.[46]

Currently, recommendations regarding the frequency of Pap testing are largely based on age and health history. General guidelines recommend that women have a Pap test beginning about 3 years after they begin to have sexual intercourse, but no later than age 21. Typically, they also recommend the tests be given annually to women under age 30, and every three years for women over 30 who have had three normal Pap tests three years in a row and are at low risk for cervical cancer.[47]

The screening rate for cervical cancer in the U.S. is relatively high, with 50 million Pap tests performed annually.[48,23] The result of these organized programs has had a dramatic effect; cases of cervical cancer in the U.S. plummeted by 74 percent between the introduction of the Pap test in 1955 and 1992.[8]

…BUT NOT FOOLPROOF

Despite such impressive results, cervical cancer screening has its own limitations, related to accuracy, follow-up, and patient access. Especially with older screening tools, a history of false negative results has often led to misdiagnosis. For example, one analysis estimated that only 47 percent of American women who developed cervical cancer were screened consistently in the five years prior to their diagnosis.[49]

Despite impressive results, cervical cancer screening has limitations, related to accuracy, follow-up and patient access.

Accuracy aside, patients often fail to follow-up on an abnormal Pap test result.[50] This can be the result of limited access to screening and necessary medical care, or patients simply do not adhere to their physicians' recommendations.

For economic and social reasons, such as cultural restrictions, language barriers, and low health literacy, access is especially problematic for low-income, immigrant, rural, and minority women. As a result, cervical cancer rates are much higher for these women than for the U.S. population at large. For example, African American women contract cervical cancer at twice the rate of white women.[51]

There is also alarming evidence that screening has decreased across the *whole* population: between 2001 and 2004 Pap test screening rates among women ages 18 to 64 fell from 81 percent to 76 percent. A 2005 Kaiser Family Foundation study postulates that this decline is most likely due to the inability to afford medical care or lack of insurance.[52]

EMERGENCE OF THE HPV VACCINE

Since the 1980s, when research first confirmed that a virus was responsible for cervical cancer, scientists have hoped that a vaccine could be developed to control this disease.[53] Even in the U.S., which has fairly robust cervical cancer screening programs compared to other regions around the globe, a vaccine to prevent high-risk HPV infection would be valuable, given the high transmission rate of HPV and the limitations of screening noted above.

Today, there are two products in this class of technology. Both show immense promise in preventing persistent infection with HPV subtypes 16 and 18, known to cause 70 percent of cervical cancer. GlaxoSmithKline, Inc. (GSK) has developed a bivalent vaccine Cervarix®, which protects against two HPV subtypes: 16 and 18. Merck & Co.'s quadrivalent vaccine, Gardasil®, protects against the subtypes 16 and 18, as well as 6 and 11, the latter two of which cause 90 percent of genital warts.

Merck's product recently received approval from the Food and Drug Administration (FDA) for use in females, ages 9-26; GSK expects to file with the FDA by the end of 2006.[54] Research indicates that in order to be most effective, the HPV vaccine should be administered to females prior to becoming sexually

active.[55] Because exposure to HPV occurs soon after sexual activity commences and because it begins early – only 3.7 percent of females have had sexual intercourse before age thirteen, but this rate jumps to 29.3 percent by 9th grade – experts have identified the target population for these vaccines to be females ages 11-12.[56] And since the vaccine is still effective for sexually active females, they also designated 13 to 26-year old women as a crucial catch-up population.[57,58]

Adding the HPV vaccine will reduce cervical cancer rates beyond what had been thought possible through screening alone.

Importantly, because this generation of vaccine will *not* protect against all high-risk HPV types, women will still need to have regular cervical cancer screening. However, adding the HPV vaccine will reduce cervical cancer rates beyond what had been thought possible through screening alone.

THE HPV VACCINE HAS HIGH VALUE POTENTIAL

Over the past few months, there has been a flurry of scientific and media attention focused on the great promise of the HPV vaccine. Our research indicates that this enthusiasm is justified. Not only have clinical trial results demonstrated effectiveness, but preliminary studies also suggest that the vaccine will be cost-effective as well.

Clinical Trials Show Nearly 100 Percent Efficacy

In published Phase II efficacy trials, the HPV vaccine was tested in large, randomized, controlled, double-blind placebo studies in approximately 1,700 sexually active, older adolescent and young adult women.[59] Over the course of roughly two years, the quadrivalent vaccine was 86-89 percent effective and the bivalent vaccine 100 percent effective in preventing persistent infection with HPV subtypes 16 and 18.[9,10] Both vaccines were nearly 100 percent effective in preventing precancerous lesions.[11] Early indications from Phase III trial data for the quadrivalent vaccine, a study that included over 12,000 women, confirmed the efficacy of the vaccine and its ability to prevent precancerous lesions associated with HPV subtypes 16 and 18.[60]

The HPV Vaccine Is Cost-effective

Given the clinical trial results, patient outcomes for the HPV vaccine are very promising. Preliminary economic analyses have shown the HPV vaccine to be cost-effective as well.

Newer vaccines coming to the market are typically more expensive and less likely to be cost-saving than older vaccines, such as influenza. As a case in point, the HPV vaccine is likely to be the most expensive vaccine ever to hit the U.S. market (for a three dose series, the costs are estimated at approximately $360).[61] Therefore it is essential to examine the *value* of these new vaccines in terms of their overall impact on health outcomes and quality of life, how these compare against costs and how those comparisons stack up against other options. The most common form of analysis used for this purpose, cost-utility analysis, compares the costs and

quantified quality of life effects (represented by Quality Adjusted Life Years, or QALYs) for the use of a new treatment, relative to the previous standard of care.

To date, four independent cost-effectiveness studies on the HPV vaccine have been published.[12,13,14,15] Using cost-utility analysis, all of them investigated the clinical and economic impacts of an immunization and screening program targeting high-risk HPV in adolescent females. When compared to current cervical cancer prevention through screening and treatment, all of these studies found that a prophylactic vaccine targeting high-risk HPV subtypes decreased cervical cancer risk by 46 to 66 percent and increased quality-adjusted life expectancy. For example, compared to screening alone, a 12 year-old adolescent vaccinated against HPV who followed current screening standards would gain one year of quality life (QALY) at a cost of between $14,600 - $24,300.[iv,62] (For more information on HPV vaccine cost-effectiveness analyses, see Appendix 1.)

According to the literature on cost-effectiveness analysis, treatments that buy a year of quality life for less than $25,000 are considered very cost-effective.[63] So, by this standard, the HPV vaccine is likely to be even *more* cost-effective than other recommended vaccines that have already been successfully adopted, such as the pneumococcal conjugate vaccine.[64,65]

However, such measures of cost-effectiveness are only a *baseline* measure of value. Additional potential benefits from the HPV vaccine not addressed by these studies, such as the decrease in other HPV 16 and 18-related cancers and the avoidance of psycho-social impacts of contracting an HPV-related condition, would only increase the vaccine's value even further.

Over time, even more information will be available on the economics of this vaccine. At least one author is already working on updated economic estimates that incorporate new trial data on the HPV vaccine, the impact of herd immunity, and a broader target population, including males and a wider range of ages.[66]

While these new analyses and the additional benefits they are likely to show will further underscore the value of the HPV vaccine, the vaccine already weighs in as a sound investment for the U.S. public health system.

MOMENTUM IS BUILDING

Many stakeholders have already embraced the HPV vaccine and are actively engaged in bringing it to market and driving its adoption. With a potential global market of $4-7 billion per year by 2010, there has been intense investment by manufacturers.[67] In a consolidated industry known for sole suppliers, there are already two developers of the HPV vaccine, both actively involved in promoting public awareness and organizing the stakeholders necessary to drive adoption.

[iv] Note: The base-case cost of the vaccine in these studies ranged from $200-$400.

There is positive movement in the public sector, as well. Many professional societies, local governments, and organizations that advocate for women and minorities are beginning to organize and consider plans to adopt the HPV vaccine. Even groups who were initially resistant to the vaccine, out of concern that it might encourage premarital sex or promiscuity, have come out with messages of support.[68,v] Initial research also indicates that clinicians, parents, and young adults would be likely to accept the vaccine.[69,70]

Lastly, and perhaps most importantly, the FDA's recent approval of the first HPV vaccine and the subsequent recommendations of the Advisory Committee on Immunization Practices (ACIP)[vi] appear to be major catalysts for adoption. Health insurance companies base their coverage decisions on ACIP recommendations. Clinicians also use ACIP recommendations and those of professional societies to guide their immunization practices.

Figure 2-1:

PROVISIONAL RECOMMENDATIONS OF THE ACIP

- The ACIP recommends routine vaccination of females ages 11-12 years of age with three doses of quadrivalent HPV vaccine.
- The vaccination series can be started as young as 9 years of age at the discretion of the clinician.
- Vaccination is recommended for females ages 13-26 years of age who have not been previously vaccinated.

Source: CDC

The ACIP also passed a resolution that includes the HPV vaccine in the government program, Vaccines for Children (VFC), which provides free vaccines to over 40 percent of U.S. children.[71]

The combination of clinician promotion and private and public coverage of vaccines ensures that at least a portion of the population has access to them.

CONCLUSION

A combination of scientific ingenuity, public and private investment, and a range of additional support from the scientific and public health communities has managed to advance the HPV vaccine from concept to public health reality. These same forces will continue to play critical roles in driving the dissemination of the vaccine. Yet despite these important drivers, there are significant barriers in the financing, delivery, and acceptance of immunizations. These obstacles threaten not only the HPV vaccine, but also the many other promising vaccines in the pipeline.

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[v] The majority of these groups are not, however, in support of any measure that would make the HPV vaccine mandatory.

[vi] 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 most effective means to prevent vaccine-preventable diseases (Source: ACIP web site).

Hence, it seems likely that if stakeholders fail to take up the call to action of the HPV vaccine, these issues will continue to hinder the vaccine enterprise and the development of innovative products to improve public health.

Significant Barriers to Adoption

While the HPV vaccine's efficacy and value are compelling, this vaccine, like others, faces formidable barriers to adoption. If the past is any indication, the initial adoption of the HPV vaccine will be poor in both the adolescent target population and the young adult catch-up population. Already 35 million adolescents do not receive one or more recommended vaccines, and adults have historically had poor immunization rates.[72,73] In the absence of additional policies to support immunization, expert analysis suggests that once each HPV vaccine is licensed and recommended by ACIP, the adoption rate of the full three doses by the target population is likely to be as low as 15 percent within the first year.[74]

To ensure the successful adoption of the HPV vaccine, the three main challenges of financing, delivery, and public acceptance must be addressed.

The adoption of the HPV vaccine in populations that suffer disproportionately from cervical cancer – immigrants, minorities, those of lower socioeconomic status, and women residing in rural areas – will be especially difficult. Health experts predict that cultural restrictions, language barriers, and low health literacy, which tend to be prevalent among these groups, will further discourage their access to the HPV vaccine and worsen existing health disparities.[74]

To ensure the successful adoption of the HPV vaccine across all subsets of the population, the three main challenges of financing, delivery, and public acceptance must be addressed.[75]

PATCHWORK FINANCING LIMITS VACCINE ACCESS AND CREATES DISPARITIES

Individuals are highly price sensitive to vaccines; studies have shown that even modest prices or co-pays reduce immunization rates.[76] Furthermore, under- and un-insurance have been associated with lower immunization rates.[16] Therefore, adoption of vaccines appears to be highly dependent upon adequate coverage. Yet the current financing system for adolescents and adults is a patchwork of private and public coverage that leaves gaps in access to immunizations for many individuals.

Public Financing Gaps for Adolescents and Adults

The U.S. has a fairly robust public program that provides vaccines to eligible children under the age of 19. An estimated 57 percent of eligible children receive vaccine coverage through a combination of state and federal funding.[77]

The cornerstone of this public funding is the Vaccines for Children (VFC) program, which provides free immunizations to children who are Medicaid eligible, uninsured, American Indian/Alaskan Natives, and underinsured (See

Sidebar: Financing the HPV Vaccine).[vii] Yet this program has limitations. Under the VFC, vaccine administration costs are covered in large part by state Medicaid programs, which are always vulnerable to cuts in state budgets. The underinsured can receive VFC vaccines through federally qualified health centers (FQHCs), or sometimes only through rural health centers. But having to travel to these sites results in an additional burden on parents and disrupts continuity of care.

Those not eligible for VFC have similar issues. For example, they might be covered through State Children's Health Insurance Programs (SCHIP) or other programs funded from state budgets or the federally funded Section 317. Yet these programs are struggling with budget cuts, a dramatic rise in the number of recommended vaccines, and the higher costs of new vaccines. North Carolina, for instance, spends $11 million annually to provide universal vaccine coverage to all children from birth to age 18. The HPV vaccine alone could cost North Carolina at least another $10 million.[78]

For many states, a likely funding short-fall will result in disparities, where individuals who are VFC-eligible receive immunizations, while children covered by other government programs do not.[79] For example, due to its high cost, several universal coverage states elected to exclude the pneumococcal conjugate vaccine from their programs that provide vaccines to children ineligible for VFC.[80] It seems likely that similar decisions may be made for the HPV vaccine, unless public financing for vaccines is significantly increased.

Public funding for immunizing young adults, however, is virtually non-existent. There is no mechanism similar to VFC for uninsured adults, SCHIP coverage usually ends by age 19, and Medicaid only covers some adult vaccines.[81] This presents a significant problem, since over 30 percent of young adults lack health insurance. In addition to the difficulty of paying for the out-of-pocket costs of the HPV vaccine, individuals without insurance are also less likely to have contact with a health care clinician who is their main source of information about immunizations.

Cost-sharing and Underinsurance Limit Coverage through Private Financing

Private insurance plays an important role in vaccine coverage, especially for children. Most health insurance plans do provide some coverage for immunizations, especially childhood vaccines, if strongly recommended by ACIP and professional societies. Yet, a significant minority of private plans does not provide coverage for adult and adolescent vaccines, and many plans require patient cost-sharing.[82] Other sources have estimated that as many as 10-30 percent of adolescents and adults have forms of private insurance that do not provide coverage for vaccines.[16] Experts are concerned that the high cost of HPV and other innovative vaccines, even if they are demonstrated to be cost-effective, will only exacerbate this existing problem.[16,83]

[vii] For the purposes of the VFC, an underinsured child is defined as one with health insurance coverage that does not include vaccinations.

Financing the HPV Vaccine for Children and Adolescents

Vaccine coverage in the United States is made up of a patchwork of federal, state, and private financing. As shown in Figure 3-1, for children under the age of 19, there are five sources: the federally-funded Vaccine for Children program (VFC), private insurance, out-of-pocket spending, state budget allocations, and federal budget allocations made under Section 317 of the Public Health Service Act (known as "Section 317 funds").

Approximately 40 percent of children, who fall below the poverty line and/or are members of certain minority groups, have their vaccines funded through the VFC program. At the other end of the spectrum, there are approximately 45 percent of children who receive their vaccines through private insurance or out-of-pocket spending. Caught in the middle are the remaining 15 percent who are beholden to fluctuating levels of Section 317 funding, which is appropriated annually through Congress, and to state budgets, which can also vary year-to-year.[84,85]

Fluctuations in Section 317 funding and in state budgets result in gaps among a segment of children who neither meet the VFC criteria, nor have private insurance or personal funds to cover the cost of vaccines on their own.

To address this problem, experts have long recommended large increases in Section 317 funding. And, since Section 317 is already under-funded, each new vaccine, like HPV, only puts further stress on an already strained system.

Analysis estimates a shortfall of $60 million in 2007 Section 317 funds to purchase recommended vaccines – not including many of the recently recommended vaccines, including HPV. To immunize 15 percent of female adolescents (ages 11-18) against HPV in 2007 would require an additional $54 million in Section 317 funding. Reaching a target 80 percent immunization rate for this same population over five years would require an additional increase of $363 million.[86]

While this analysis is based on conservative estimates, it clearly illustrates the financial challenge that lies ahead. Unless Section 317 is increased significantly, large numbers of adolescents will fall through the cracks and go without access to the HPV and other life-saving vaccines.

Fortunately, there is some momentum to increase Section 317 funding: the House allocated a significant increase in Section 317 funding in the FY 2007 budget.[87] To increase access, stakeholders should work together to ensure that this proposed increase passes.

Figure 3-1:

VACCINE FINANCING SOURCES FOR CHILDHOOD AND ADOLESCENT IMMUNIZATIONS			
Financing Mechanism	Source	Eligibility	Stability
Vaccines for Children	Entitlement program funded through Medicaid, managed by CDC	Under age 19 and Medicaid-eligible; uninsured; Alaska native or American Indian; or underinsured served by FQHCs	Stable funding stream
State	State budget appropriations	Varies by state	Significant fluctuations
Section 317	Discretionary appropriation approved by U.S. Congress	No restrictions; priority on childhood immunization	Significant fluctuations
Private Insurance	Private insurance or employer-self insurance	Dependent on plan; most plans cover recommended childhood immunizations	Dependent on ACIP and professional society recommendations
Out-of-Pocket	Individual	NA	NA

Although a few insurance companies have already stated that they will cover the HPV vaccine, the vaccine's high cost might result in higher cost-sharing and/or restrictions being placed on coverage.[88] To finance the inclusion of the vaccine within a plan, private insurers may increase cost sharing through higher premiums and increased co-pays. Others may choose to restrict coverage to certain populations, or eliminate coverage altogether.[89,90]

INADEQUATE DELIVERY SYSTEM HINDERS MASS IMMUNIZATION

As indicated, the U.S. health care system is not structured to handle the widespread immunization of adolescents and young adults. The primary challenges are the lack of a "medical home,"[viii] infrequent preventive health care visits, limited tools for tracking patient immunization histories, and clinician overhead costs.

The U.S. health care system is not structured to handle the widespread immunization of adolescents and young adults.

Adolescents Lack a Medical Home and a System of Preventive Visits

Adolescents and young adults are a challenging group to immunize, since many do not receive regular preventive care within a "medical home."[91,92] This is despite the recommendations of medical professionals who have long argued that comprehensive, continuous care allows physicians to more easily address prevention, including immunization. Individuals without this kind of medical home often turn to emergency departments, where acute, rather than preventive, care takes precedent.

Although most adolescents, especially younger adolescents, have at least one medical visit annually, many clinicians fail to take advantage of this opportunity to immunize patients. One study estimates that less than half of all clinicians routinely check adolescent immunization records during sick visits.[93]

Given the paucity of visits and the lack of focus on immunization, it will be extremely challenging to ensure that adolescents receive all three doses of the HPV vaccine within the recommended six-month dosing regimen.[94] Data suggest that only 11 percent of adolescents visited their pediatricians three times over two years – let alone during a six-month interval that would be needed for the HPV vaccine.[95]

There are few data on immunization rates among young adults. Data for older adults show their immunization rates to be quite low – this is especially true amongst populations that are medically underserved: the economically disadvantaged, rural populations, inner city populations, and minorities. Many experts believe that a lack of well-established preventive visits and opportunities

[viii] A medical home is a health care setting that is "accessible, continuous, family centered, coordinated, compassionate, and culturally effective."

for immunization within our current health care delivery system is a significant contributing factor.[96]

Systems to Track Immunization Rates Are Poor or Absent

Our current health care delivery system also lacks widespread use of modern tools needed to track today's adolescent and young adult immunizations. The most important of these are immunization registries, which are confidential, population-based, computerized systems for maintaining information regarding children's vaccinations.[97]

Electronic registries and electronic medical records are not widely adopted and where available, are underused by clinicians.[98] Without such systems in place, it is difficult to know who has or hasn't been immunized, which patients and clinicians need reminding, what the trends are with state and national immunization rates, and what needs to be done to improve these rates.[99]

The U.S. is just beginning to consider tracking adolescent immunization on the national level. State immunization registries are already working to track children, but they've only started to track adolescents and adults.[100] However, there is still a lot of work to be done just for children. Data show that only 39 percent of private immunization clinicians are actively submitting data to these registries and less than half of all children are enrolled in them.[101]

Clinicians Struggle with Insufficient Reimbursement and High Overhead

Clinicians are one of the most important sources for immunizations.[102] Yet poor reimbursement rates, coupled with high overhead costs, pose significant barriers to the adoption of the HPV vaccine within the clinician's office.

In fact, clinicians often find that the reimbursement from immunization is simply inadequate to cover the cost of purchasing, storing, and administering vaccines.[103,104,105] The lack of electronic data described above also makes it difficult for clinicians to determine patient eligibility, complicating paperwork.[106] Moreover, some health plans require modifications to a clinician contract with each new vaccine. This can delay coverage well past the time a new vaccine is recommended.[107]

The higher the costs associated with a particular vaccine, the greater the potential burden on clinicians. Indeed, a recent study found that some clinicians were slow to adopt the high-cost pneummococcal conjugate vaccine in part due to high, upfront purchase costs.[108,109] Faced with this dilemma, the clinicians studied often chose to refer patients to vaccine clinics, which resulted in discontinuity of care and possibly delayed or missed immunization.[106] Again, similar scenarios are expected to play out with the HPV vaccine.

REGIMEN AND COMMUNICATION CHALLENGES ARE BARRIERS TO PUBLIC ACCEPTANCE

Although evidence suggests that adolescents, parents of adolescents, and young adults would accept an HPV vaccine if it were available, the demanding dosing schedule and communication challenges pose barriers to public acceptance.

HPV Immunization Regimen Is Demanding

Weaknesses in our current health care delivery infrastructure make it challenging to administer a full course of the HPV vaccine over a six-month period. First, as noted, for many within the target group, it is often hard enough to get to the doctor's office for an annual well visit. Now imagine that adolescents – and in many cases, their parents – are suddenly being asked to visit their doctor's office three times within a six-month period in order to get the full series of shots. Just the logistical barriers, such as travel time, out-of-pocket costs, and consent laws, are likely to make this problematic.

What's more, most three-series vaccines, like hepatitis B, are traditionally given as part of frequent well-baby visits, which are structured to coincide with immunization needs. Without such a system in place for adolescents, the burden will be on patients and their parents to provide the motivation to complete the full course of the HPV vaccine.

Public Is Uninformed of HPV Risks and the Need for Immunizations

Another challenge facing HPV vaccination is the fact that the public – including patients, parents, and adolescents – has little knowledge about HPV and its risks. One study demonstrated that less than half of all women in the U.S. have even heard of HPV, and less than 25 percent understand that HPV is the primary cause of cervical cancer.[110] In addition, there is a great deal of confusion regarding the types of HPV, the personal risk for HPV infection, the fact that the virus leads to cervical cancer, and the purpose and need for continued screening once vaccinated.[111] Much of the information that is available is incomplete, difficult to comprehend, or simply inaccurate.[112]

Less than half of all women in the U.S. have even heard of HPV, and less than 25 percent understand that HPV is the primary cause of cervical cancer.

This limited knowledge makes it difficult for the public to appreciate the value of the HPV vaccine. And this, in turn, makes people less likely to voluntarily seek out immunization. Further complicating public acceptance of the HPV vaccine is that most individuals do not know what vaccines they need or have misconceptions about vaccine safety.[102]

As noted above, health care clinicians, who are otherwise such an important source of information, often fail to use adolescents' limited encounters with the health care system to review and recommend immunizations. This may, in part, be due to competing priorities, such as an illness or injury, and in part due to their lack of knowledge about immunization schedules and contraindications.[98] Experts believe that in the case of HPV, clinicians might fail to recommend immunization simply because of limited knowledge about the disease, or due to their reluctance to discuss sexual health with younger adolescents or pre-teens.[113,114]

CONCLUSION

The HPV vaccine is a highly valuable innovation that has the potential to reduce the risk of cervical cancer for millions of young girls and women. Although many stakeholders are already hard at work driving the widespread adoption of the vaccine, significant barriers remain, including financing issues, a weak health care delivery infrastructure, and limited public awareness. Importantly, these same challenges also represent an opportunity for vast improvements that are needed by the entire vaccine system.

Call to Action

A CALL TO ACTION FOR THE HPV VACCINE AND FUTURE VACCINES

As noted, the barriers to adopting the HPV vaccine are in many cases no different than those facing most vaccines. Hence, facilitating the adoption of the HPV vaccine presents an opportunity not only to promote a breakthrough in cancer prevention, but also to fix much of what ails the U.S. vaccine enterprise.

Facilitating the adoption of the HPV vaccine presents an opportunity to fix much of what ails the U.S. vaccine enterprise.

Overcoming these formidable barriers will only occur if all the stakeholders involved with vaccines work together to address the three main barriers standing in the way of progress: insufficient financing, the inadequate health care delivery system, and the lack of public awareness. This needs to be done for the success of the HPV vaccine and future vaccines, but most importantly for the future of our nation's public health.

To address these barriers, we propose three cross-cutting solutions:

1. **Harness public support through both wide-scale and targeted education campaigns.** A well-informed and impassioned public can drive increases and expansions in the financing of vaccines and improve their acceptance and adoption.

2. **Strengthen the vaccine delivery system within our current health care system.** For vaccines to be successful, particularly those targeted at adolescents and young adults, we need a delivery infrastructure, tools, education, and incentives that fully support immunization recommendations and goals.

3. **Continue to expand the vaccine delivery system to include alternative sites.** For large-scale immunization programs to be successful, we must expand delivery beyond the clinical setting and find additional venues that are convenient for patients and families and appropriate for immunization.

HARNESS PUBLIC SUPPORT THROUGH WIDE-SCALE AND TARGETED EDUCATION CAMPAIGNS

Harness public support through wide-scale education campaigns

First and foremost, we recommend a broad campaign to promote the value of vaccines. For many vaccines, including HPV, the barriers to financing and public acceptance are rooted in the limited importance that the public places on immunization today. The goal of this proposed education campaign is to generate wide-spread awareness and appreciation of the importance of vaccines to our public health.

What Is Needed

For a broad education campaign to be successful, we believe that leadership needs to come from the National Immunization Program (NIP), a division of the U.S. Centers for Disease Control and Prevention (CDC). In turn, we recommend that the NIP create a coalition of supporters with aligned interests, including state health departments, vaccine advocacy groups, public health organizations, vaccine manufacturers, and others. This coalition could pool funds and use them to hire a major public relations or social marketing firm to develop and execute a campaign.

An added benefit of such a coalition is that it could speak with one voice. Consistency is particularly critical, given the range of misconceptions that have made their way into public attitudes.

To emphasize the value of vaccines, a series of messages should reiterate real stories that may have been forgotten, like the mid-century triumph of the polio vaccine. Other messages could focus on educating the public to take personal responsibility for ensuring that each of us has had all of our recommended immunizations. Still others could focus on the need to make vaccines accessible and affordable to everyone, not only for the sake of individual benefit, but also to enjoy the advantages of herd immunity.

The public needs to be reminded that everyone has the personal responsibility of obtaining their needed immunizations in order to maintain disease control and to protect those who are unable to be immunized. The recent measles outbreaks could serve as an example to emphasize this point.[115] Finally, special attention must be placed on promoting the safety of vaccines, to counteract the unsubstantiated claims of some groups that vaccines cause neurological problems such as autism.

In developing this campaign, the coalition should work to ensure that messages are culturally relevant, translated into a variety of languages, and are written at a reading level accessible to the widest possible audiences regardless of ethnicity and socioeconomic level. In particular, experts recommend targeting messages to mothers, as they tend to be the primary decision makers regarding family health.

We recommend a variety of methods and channels to disseminate messages as broadly as possible. Public service messages can be broadcast on mass media outlets such as TV, Internet, podcasts, radio, billboards, home mailings, magazines, newspapers, and public transportation. Distribution should also focus on locations where the public congregates such as shopping malls, movie theaters, community centers, religious organizations and grocery stores, as well as in doctors' offices, clinics, and pharmacies.

Experts have suggested that responsible public advocacy be used to increase and expand vaccine financing. Specific actions to target include: reversing recent budget cuts and increasing allocations for Section 317 and state-level vaccine programs, and persuading employers and private payers to improve vaccine coverage by providing "first dollar" coverage of vaccines and removing co-pays.[116]

Once there is the public support and political will to adequately finance vaccines, a good next step would be to expand current programs to fill gaps in coverage. For example, some have advocated increasing the eligibility age of the Vaccines for Children program to age 21 to include the older adolescent and young adult population, who typically fall through the cracks.

Ultimately, a blanket, public program that would provide immunizations to all needy individuals who cannot otherwise be served in the private insurance market – regardless of age – would go far in improving vaccine financing and ensuring high immunization rates. Such an approach could be modeled after the successful Vaccines for Children program.

Harness public support through targeted education campaigns

While it will take a wide-scale campaign to improve the appreciation, adoption and financing of all vaccines for the benefit of our public health, it is equally important to ensure that appropriate targeted campaigns are created. This is particularly critical for new classes of vaccines, like HPV, that target specific segments of the population.

What Is Needed

In developing a targeted education campaign, messages must help adolescent girls, young women, and parents alike to understand the true risk of contracting cervical cancer through exposure to the virus, how that exposure can occur, and the power of this vaccine to mitigate the threat. Since the HPV vaccine will not protect against all HPV types or other sexually transmitted diseases, it will also be important to pair this message with one that reminds of the need for continued cervical cancer screening.

For parents of younger adolescents, experts have suggested stressing the importance of cancer prevention and how commonly the virus is contracted once sexual activity begins.[117] These targeted messages should be disseminated in locations that adolescents and young women frequent, such as malls, salons, grocery stores, and health clubs.

Since significant health disparities exist among racial and ethnic minorities for both immunizations and cervical cancer screening and treatment, special attention must be placed on reaching these populations. Focus groups and translational research should be conducted to develop messages that take into account the needs and preferences of these groups and to determine the best methods to increase their likelihood of actually receiving the HPV vaccine.

As with the broader education campaign, stakeholder collaboration is needed here as well. It seems clear that effectiveness will depend on experts in sexual health, cancer prevention, health disparities, global health, women's health, and infectious diseases, along with manufacturers, working together to maximize resources and develop consistent messages. Collaborations, such as the National Cervical Cancer Public Education Campaign have already begun this important work; groups

interested in promoting the HPV vaccine will better achieve their goals by coordinating their efforts with emerging campaigns.[118]

STRENGTHEN VACCINE DELIVERY SYSTEM WITHIN CURRENT HEALTH CARE PRACTICES

Improving the delivery infrastructure for the HPV vaccine and other vaccines must begin in the clinician's office, where individuals have a consistent relationship with a health care clinician who has access to medical records and where health plans are most likely to provide coverage. It must also move upward and outward, across the entire system, building strength through comprehensive improvements, like advanced management and tracking technologies and better professional incentives.

More specifically, we recommend four critical components to strengthen our current system: institutionalizing preventive visits for adolescents and young adults, educating clinicians about the importance of vaccines for adolescents and young adults, leveraging technology and tools for tracking immunizations, and aligning appropriate incentives for immunization.

Institutionalize preventive visits for adolescents and young adults

For a long time, the public and the health care community have perceived adolescence and early adulthood as the "healthy years" where little preventive care is needed. With the advent of the HPV vaccine, together with the tetanus, diphtheria and pertussis (Tdap) booster, the hepatitis B vaccine, and the meningococcal meningitis vaccine, there is now a defined set of immunizations targeted to adolescents, whose benefits are critical and which could be bundled for delivery during regular, preventive care visits.

The goal would be to make immunization at all ages the same kind of priority it is for young children. For children, preventive care visits have been built directly into our health care infrastructure and, in fact, many of the visits themselves coincide with immunization schedules. Such a system needs to be expanded to the adolescent and young adult population.

What Is Needed

Professional societies like the Society for Adolescent Medicine (SAM) and adolescent health departments of major academic medical centers need to take a stronger role in working directly with clinicians and payers to institute a preventive care platform for adolescents.

Our research indicates that building an infrastructure for adolescent and young adult vaccines can best be achieved through a multi-pronged approach that includes education, incentives, and support systems. Specific recommendations, developed by SAM, include developing a platform for adolescent vaccines by designating three sets of preventive visits that focus on immunization, one set at ages 11-12, for initial immunization (such as HPV), and the other two sets at ages 14-15 and 17-18 that could be used to administer any newly recommended vaccines.

To ensure the completion of the HPV vaccine's three-dose series within the six month period required, this platform must be supported with tracking tools and recall/reminder systems, as described below.

Educate clinicians about the importance of vaccines for adolescents and young adults

As noted, many clinicians miss opportunities to immunize adolescents and young adults. With the advent of the HPV vaccine and other emerging vaccines that are also targeted at adolescents, clinicians will need significant education about all of them.

What Is Needed

To educate clinicians, professional societies must quickly develop and disseminate information on good immunization storage and practices. For HPV, this must include guidance on specific disease and vaccine facts, as well as on how to approach communicating with adolescent and young adult women about sexual health.[119]

This information can be delivered via guidelines, peer reviewed journals, websites, thought-leader endorsements, conferences, and continuing medical education. Particularly for the HPV vaccine, it is critical that this information get to clinicians as soon as possible, so that they are prepared on vaccine practices, as well as on how to discuss the HPV vaccine with their patients, as soon as the products become available.

Leverage technology and tools for tracking immunizations

Today, we are greatly under-leveraging technology and tools to track immunizations at the individual and population levels. State vaccine registries are under-utilized and most do not include adolescents.

What Is Needed

Clinicians, state public health departments, and the CDC must renew their commitment to supporting, enhancing, and populating state vaccine registries and expanding them to include adolescents. Special attention must be paid to reducing redundant data entry. Ideally, this would be ensured by integrating the registries with in-office, electronic medical records.

Clinicians, in particular, must work to improve immunizations within their own practices. To this end, we recommend implementing patient reminder or recall systems, issuing standing orders which stipulate that all children and young adults meeting certain criteria should be vaccinated no matter the reason for the health visit, administering multiple vaccines where possible, and regularly assessing practice performance on immunizations.[120]

The single most important tools to assist with these endeavors are state vaccine registries. Registries can be used to generate patient reminders, provide real-time clinician decision support, track immunization rates within a practice to target improvement, and even track adverse events.

Since registries are only as effective as their inputs, there again appears to be a clear need for system-wide cooperation. The CDC and state public health departments must strengthen their commitment to enrolling private clinicians and providing the training necessary to ensure that these individuals can efficiently and effectively utilize the registries. In turn, clinicians must commit to using the registries to better manage immunizations within their patient populations.

To implement these recommendations, stakeholders, such as professional societies and state health departments should use resources that are already at hand. For example, the American Immunization Registry Association is already organizing work groups on topics such as data exchange and is publishing best practices on improving clinician participation in registries.[121]

Institute appropriate incentives for immunization

Given the increasingly high up-front costs of purchasing vaccines and the historically low rate of reimbursement for vaccine administration, there has been little alignment between incentives for clinicians to administer vaccines and the public's need for immunizations. Fortunately, there are two emerging solutions that can help mitigate this problem: increased reimbursement and pay-for-performance.

What Is Needed

Increased reimbursement for vaccine administration will serve as an incentive for clinicians to provide immunization. In 2006, Medicare published vaccine administration codes with higher reimbursement values than previously paid.[122] While most vaccines are not targeted at the Medicare population, private payers often use Medicare rates to set their own reimbursement rates for services.

To capitalize on these recent increases in reimbursement rates, clinicians must be made aware of the change and professional societies must work with private payers to adjust their rates to reflect Medicare's increases as soon as possible.

Another emerging solution that will help align clinicians' incentives with health care priorities is pay-for-performance programs that financially reward clinicians for high immunization rates. As use of pay-for-performance programs proliferate, clinicians and payers must ensure that adult and adolescent immunizations are included as a component of their performance measures.

CONTINUE TO EXPAND VACCINE DELIVERY SYSTEM TO INCLUDE ALTERNATIVE SITES

While it is important to strengthen the delivery of immunizations within the clinician's office, we must also expand delivery beyond the doctor's office with additional immunization sites. These should be convenient and appropriate for delivering the HPV vaccine and other vaccines that are targeted at adolescents and young adults. Solutions include expanding adolescent and young adult immunizations into existing immunization venues, such as schools, pharmacies, and urgent care sites and into non-traditional venues, such as community centers or malls.

Expand existing immunization venues

Schools, pharmacies, and urgent care sites all have experience administering vaccines. Schools have traditionally focused on mandatory immunizations for young children, while pharmacies and urgent care sites have focused primarily on delivering the influenza vaccine. By expanding their respective foci, each kind of site could be an effective venue for delivering important vaccines to adolescents and young adults.

What Is Needed

School-based immunization programs have been identified by experts as the most effective voluntary intervention that can be used to increase the rate of immunizations for adolescents. And that's because a) schools are the most efficient way to capture a large audience of adolescents, and b) school-based programs relieve parents of the hassle of making multiple visits to a clinician's office.

As a respected community resource, school programs also present an opportunity to educate parents about the importance of immunization for all members of the family. Moreover, programs for students entering middle school, high school, and college align well with the Society of Adolescent Medicine's three targeted age groups. They could, therefore serve as appropriate immunization check points and catch-up, if required. To maximize these programs, schools should offer *all* recommended adolescent vaccines to their students, not just the HPV vaccine.

Community health departments must take the lead in handling administration and financing, as most schools have limited time and resources. To overcome potential barriers such as consent, parents, clinicians, teachers, school administrators, and policy makers must work together to establish appropriate voluntary programs.

Here again, immunization registries will play an important role. We believe that only by using effective registry systems – preferably electronic – can new immunization programs, like those for HPV, be successfully implemented. At the very least, paper records will need to be sent to clinicians, and states must work to address barriers to record sharing that are currently posed by the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and the Family Educational Rights and Privacy Act of 1974 (FERPA).[123]

There are several successful examples of school-based immunization programs for the hepatitis B vaccine that could be used as models for future efforts. A notable program is the private/public partnership that was organized in Baton Rouge, Louisiana, which successfully immunized over 3,400 students – 76 percent of those eligible.[124]

In addition to voluntary programs in schools, use of two, additional, alternate sites for immunizations should be expanded: pharmacies and urgent care centers. Pharmacies, which have long had experience distributing the influenza vaccine, are ideally positioned to expand their offerings to include a greater number of immunizations. In addition, emerging convenient medical care sites, such as MinuteClinics®, which are located at malls and within large retailers like Target®,

should promote that they offer vaccines and also expand their offerings to include new vaccines for adolescents and young adults.

Expand into non-traditional venues

To further make wide-scale immunization convenient and easy, we recommend that employers, faith-based organizations, and service groups such as Big Sisters Association, Kiwanis, and Rotary Club play a role. We suggest that these groups provide education to their constituents and sponsor immunization drives and mobile clinics. Similarly, malls and community centers that offer after-school programs to youths and young adults are also strong candidates for immunization sites.

What Is Needed

To reach adolescents specifically, efforts should target places where they tend to congregate, such as malls, parks, shopping centers, and community recreational centers. To be successful, they must consider how to coordinate with immunization registries to ensure continuity of recordkeeping and be structured in such a way that they can provide a full course of immunizations.

CONCLUSION

Vaccines have been, and will continue to be, immensely valuable public health interventions. Due to constantly evolving health threats and the emergence of new diseases like SARS, HIV, and new strains of influenza, the chronic gaps in our immunization system have received renewed attention by government officials, policymakers, and the public. A number of these flaws, from vaccine financing to challenges with the delivery infrastructure and public education, are well illustrated by the challenges facing the HPV vaccine.

Poised to help millions of women prevent cervical cancer, the new HPV vaccine is extremely promising. Yet its outlook demonstrates that there are important issues that need to be tackled to ensure its full adoption and that of all vaccines. Unless we take up the call to action to address the challenges of our beleaguered system – in financing, delivering, and adopting vaccines – the immense benefits of this vaccine, and future vaccines, will not be realized.

APPENDICES

Appendix 1: Cost-Effectiveness Analysis

The goal of the *Innovations Series* is to identify opportunities to accelerate the adoption of highly valuable medical innovations that will benefit patients and help contain U.S. health care costs. When assessing a new innovation – a drug, device, or method of care delivery – NEHI first analyzes its value and, if promising, makes recommendations to accelerate its adoption. Cost-effectiveness is one indicator that NEHI uses in assessing the value of medical innovations, but we also consider other factors such as such as convenience and difficult-to-quantify, quality-of-life benefits.

In determining the value of the HPV vaccine, NEHI started with a review of available cost-effectiveness analyses. Through discussions with experts and a review of the literature, (we identified five sources: four independent, published cost-effectiveness studies on the HPV vaccine[12,13,14,15] and one unpublished study in progress.[127] All studies investigated the clinical and economic impacts of an immunization and screening program targeting high-risk HPV subtypes in adolescent females.

When compared to current cervical cancer prevention through screening and treatment, the four published studies found that a prophylactic vaccine targeting high-risk HPV subtypes decreases cervical cancer risk by 46 to 66 percent and increases quality-adjusted life expectancy. Further, these studies found the HPV vaccine to be cost-effective, albeit to differing degrees ($14,600/QALY - $24,300/QALY, compared with current screening).[125] The differences in clinical and economic outcomes across studies largely stem from the types of analyses performed – static versus dynamic disease transmission models – and from assumptions regarding the vaccine's impact and use.

Three of the published studies by Goldie et al. (2004), Sanders and Taira (2003), and Kulasingam and Myers (2003) performed cost-effectiveness analyses using static Markov models.[12,13,14] These models are helpful in setting a conservative estimate of cost-effectiveness since they did not simulate the vaccine's ability to reduce HPV transmission (which results in herd immunity) and any associated cost-savings. For example, the study by Goldie et al. found a 16/18 HPV vaccine with 90 percent efficacy buys a quality-adjusted year of life for $24,300.

Dynamic models, on the other hand, include transmission effects and any resulting cost-savings. Two studies to date, Taira et al. (2004) and Elbasha and Dasbach (in progress), have performed analyses of HPV immunization using dynamic models.[15,126,127] Including herd-immunity improves the cost-effectiveness of the HPV vaccine. Taira et al. found a 16/18 HPV vaccine with 90 percent efficacy and adopted by 70 percent of the target population resulted in $14,583/QALY. Experts we interviewed view dynamic models as better simulations of real-world conditions, but urged caution in interpreting results from these models, given the difficulty in modeling HPV transmission dynamics.

Differing assumptions about the HPV vaccine's impact and use also factored into cost-effectiveness. Table 1 provides a summary of some of the cost-effectiveness

variables and assumptions from the five studies we reviewed. Differences in the HPV vaccine's coverage, efficacy, and duration of immunity appear to most affect bottom line cost-effectiveness.

Over time, more information will be available to provide further guidance on the value of this technology. At least one of the static Markov model's authors is planning to release an updated model that incorporates new trial data on the HPV vaccine. The new model will include the impact of herd immunity and expand the target population to include males and a greater range of ages.

Other potential benefits from the HPV vaccine not included in these studies – convenience associated with immunization versus traditional prevention measures, avoidance of psycho-social impacts of contracting an HPV-related condition, and the decrease in other HPV-related cancers – may also be significant. While these new models and unquantified benefits will help to enhance the use and valuation of the vaccine, it is clear even without this additional information that the HPV vaccine is likely to be a sound investment in population health.

TABLE 1. COMPARISON OF EXISTING COST-EFFECTIVENESS MARKOV MODELS OF HPV IMMUNIZATION[128] (ASSUMPTIONS LISTED ARE BASE-CASE SCENARIOS)									
COST PER QALY (female-only immunization)	**Results**	**Vaccine cost**	**Vaccine duration/ efficacy**	**Assumed immunization coverage**	**Age at immunization**	**Cervical cancer screening type**	**Target of HPV vaccine**	**Type of Model**	**Authors (Publication Date)**
$24,300	In a context of current screening practices, a 16/18 HPV vaccine ranging in efficacy from 70 percent to 100 percent would reduce the lifetime risk of cancer by 46-66 percent.	$377 per series	Lifetime/ 90 percent	100 percent	12 years	67 percent annual 28 percent >2 years 5 percent not screened	HPV 16/18	Markov	**Goldie et al. (2004)**
$22,750	Vaccinating the present U.S. cohort of 12 year-old girls prevents 1,340 cervical-cancer deaths over the cohort's lifetime. It is also estimated that the vaccine will result in a 20% reduction in cervical cancer incidence.	$300 per series + $100 booster	10 years plus 10 years with booster/ 75 percent	70 percent	12 years	71 percent every two years	High-risk HPV types	Markov	**Sanders & Taira (2003)**
Not applicable (This study did not calculate an incremental cost-effectiveness ratio based on quality adjusted life years.)	Vaccination plus biennial screening delayed until age 24 years reduced the incidence of cancer by 83 percent and had a cost-effectiveness ratio of $45,000 per life year compared with screening beginning at age 18 conducted every three years.	$200 per series	10 years/ 90 percent	100 percent	12 years	Varies	70 percent of high risk types	Markov	**Kulasingam & Myers (2003)**
$14,583	A 16/18 HPV vaccine for 12 year-old girls would reduce cohort cervical cancer cases by 62 percent.	$300 per series	10 years and lifetime/90 percent for low-risk types 70 percent for high risk types	70 percent	12 years		HPV 6/11/16/18	Dynamic	**Taira et al. (2004)**
$728 (note: includes value of reducing genital warts)	An estimated 8 percent reduction in the steady-state cervical cancer incident rate can be achieved with a vaccine that has a 10 year duration period – a 35 percent reduction with lifetime duration.	$300 per series + $100 booster	10 years plus 10 years with booster;90 percent	70 percent	12 years	From 0.6% to 60.4% per year, varies by age, based on screening in a U.S. health plan	HPV 16/18	Dynamic	**Elbasha & Dasbach (in progress)**

Appendix 2: Expert Interviews

NEHI is very grateful to each of the experts who generously gave us their time and provided us with valuable input for our research and analyses.

317 COALITION
Amy Ford Souders, Vice President, Cornerstone Government Affairs

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Clement Lewin, PhD, Vice President, US Government Affairs and Strategy

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Louis A. Terranova, MHA, Senior Health Policy Analyst, Division of Health Care Finance and Quality Improvement

AMERICAN CANCER SOCIETY
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AMERICA'S HEALTH INSURANCE PLANS
Bob Rehm, Director, Public Health Strategies

ANTHEM BLUE CROSS BLUE SHIELD EAST
Greg Allard, PhD, Senior Analyst

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ANTIGENICS
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ASSOCIATION OF STATE AND TERRITORIAL HEALTH OFFICIALS
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Barbara Levine, Consultant, Government Relations

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AVANT IMMUNOTHERAPEUTICS

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BLUE CROSS BLUE SHIELD OF MASSACHUSETTS

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CENTER FOR ADOLESCENT HEALTH AND LAW

Abigail English, JD, Director

CENTER FOR AMERICAN PROGRESS

Shira Saperstein, Senior Fellow

CENTERS FOR DISEASE CONTROL AND PREVENTION

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Achal Bhatt, PhD, Acting Associate Director for Policy

Harrell Chesson, PhD, Health Economist

Nancy Fasano, Program Operations Branch Chief

Daniel Fishbein, MD, Senior Medical Epidemiologist

Lauri Markowitz, MD, Team Leader, Epidemiology Research and CDC Lead, ACIP HPV Vaccine Workgroup

Warren Williams, MPH, Informatics Team Lead, Immunization Registry Support Branch

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FOOD AND DRUG ADMINISTRATION - CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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NATIONAL CERVICAL CANCER COALITION

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PHYSICIANS CONSORTIUM

Hal Wallis, MD, Chairman

POPSMEAR.ORG

Christine Baze, Founder and Executive Director

PRIVATE PRACTICE

Reginald Finger, MD

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SEXUALITY INFORMATION AND EDUCATION COUNCIL OF THE UNITED STATES

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THE BALM IN GILEAD
Anafidelia Tavares, MD, MPH, Director of Women's Health

THE KEYSTONE CENTER
Mary Davis-Hamlin, Senior Associate, Center for Science and Public Policy

THE MEDICAL INSTITUTE
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UNIVERSITY OF PENNSYLVANIA
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UNIVERSITY OF ROCHESTER MEDICAL CENTER
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UNIVERSITY OF VIRGINIA HEALTH SYSTEM
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UTMB CHILDREN'S HOSPITAL
Susan Rosenthal, Director, Division of Adolescent and Behavioral Health

VAXINNATE
Alan Shaw, PhD, Chief Executive Officer

WASHINGTON DEPARTMENT OF HEALTH
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WYETH
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Lucinda Long, Vice President Global Public Policy

Laura York, PhD, Director, Scientific Affairs and Research Strategy

Appendix 3: Expert Panelists

On Thursday, April 20, 2006, the New England Healthcare Institute (NEHI) hosted an expert panel to discuss and develop potential solutions for vaccine policy challenges, using the HPV vaccine as a case study. The panel objectives were to vet NEHI's preliminary research findings, forecast the adoption rate of the HPV vaccine in their first year of availability, discuss the major challenges facing HPV vaccine adoption, and identify priority areas for action.

Christine Baze

Ms. Baze is the Founder and Executive Director of Popsmear.org, a non-profit organization based in the Boston area. At 36, she is also a cervical cancer survivor and has become a vocal activist for raising awareness of cervical cancer and opportunities to prevent this deadly disease. In early 2000, Ms. Baze left her job as a marriage and family therapist to pursue her dream of becoming a rock star. Soon after, however, she was diagnosed with invasive cervical cancer, despite annual normal Pap smear results. Fortunately, Ms. Baze beat the cancer and celebrated her two-year remission by returning to the music scene and playing a sell-out benefit concert in Boston to raise money for cervical cancer prevention. In 2003, she began taking her band on the "Yellow Umbrella" tour to raise awareness around the issue. Ms. Baze now uses her voice and her organization Popsmear.org to empower others to take action and hopefully to prevent other women from having to experience what she went through.

Joseph A. Bocchini, Jr., MD, FAAP

Dr. Bocchini is Professor of Pediatrics and Chairman of the Department of Pediatrics at Louisiana State University Health Sciences Center in Shreveport where he also serves as Chief of Pediatric Infectious Diseases and Medical Director of the Children's Hospital. Dr. Bocchini received his MD from St. Louis University School of Medicine. He completed a residency in Pediatrics at the University of Connecticut and a fellowship in Pediatric Infectious Diseases at Johns Hopkins University. Dr. Bocchini is a member of the American Academy of Pediatrics Committee on Infectious Diseases.

Daniel Fishbein, MD

Dr. Fishbein, is a medical epidemiologist at the Centers for Disease Control and Prevention. Dr. Fishbein completed his medical education at the Medical College of Wisconsin, and Internal Medicine residency and Infectious Disease subspecialty training at the University of New Mexico. He joined the Centers for Disease Control and Prevention in 1983 and spent the first eight years with the Division of Viral and Rickettsial Diseases, where he worked on the prevention and control of rickettsial diseases and rabies (both human and animal). Between 1991 and 2000, he worked in the Epidemiology Program Office on a broad range of international health epidemiology training activities. Since November, 2000, he has been with the Health Services Research and Evaluation Branch (HSREB), Immunization Services Division, at the National Immunization Program. His research interests focus on strategies to improve adult and adolescent vaccination coverage in large populations.

Lisa Gilbert, PhD

Dr. Gilbert is Senior Researcher for the American Social Health Association, (ASHA) and is responsible for conducting various program and research activities at ASHA. She designs research methods for federal, state, foundation, and industry proposals; designs and conducts a variety of qualitative and quantitative sexual health research studies including investigations of Internet data collection methods and assessments of public, patient and provider knowledge, attitude, behavior and skill levels; designs, implements and evaluates health communication interventions; and, disseminates the research results through reports, peer-reviewed publications, lay press articles, media interviews, and national and international and presentations. Areas of research specialization include: Adolescent and women's health; STD prevention (including hepatitis and cervical cancer); reproductive health/sex education and risk reduction; health education, communication and behavior change theory; and, Internet and other innovative education and evaluation methods. Prior to joining ASHA, Dr. Gilbert served as an Assistant Professor at the University of Idaho.

Elizabeth Greenbaum, MPH

Ms. Greenbaum is a Program Analyst with the Center for Prevention and Health Services at the National Business Group on Health. In fall 2005, Ms. Greenbaum managed a research project identifying how large corporations define their preventive benefits. She conducted interviews with HR personnel from the Business Group's membership organizations (Fortune 500 companies). The chief objective of this project was to determine where primary decision-makers accessed prevention-specific information and how the information ultimately (re)structured the benefit. Research findings were presented to the National Vaccine Advisory Committee and informed a recent Business Group publication, *10 Recommendations for Promoting Prevention*. Prior to joining the Business Group, Ms. Greenbaum worked as a Policy Analyst for the Maternal Child Health Policy Research Center and the U.S. Health Resources and Services Administration (HRSA) to monitor and evaluate their State Planning Grants. Ms. Greenbaum holds a Bachelor's of Arts degree from the University of Chicago in Human Development and a Master's degree in Public Health (MPH) from the University of Michigan.

Richard Haupt, MD, MPH

Dr. Haupt is Executive Medical Director in the Policy, Public Health & Medical Affairs Department of the Merck Vaccine Division. Dr. Haupt is a 1979 graduate of the University of Maryland, with a degree in biological sciences, *summa cum laude*. He then graduated from Harvard Medical School in 1983. He completed his internship and residency at the Children's Hospital of Philadelphia in Pennsylvania and was the Chief Resident there in 1986-1987. Dr. Haupt received his Masters in Public Health from Johns Hopkins Bloomberg School of Public Health. After completing his pediatric training, Dr. Haupt was a practicing pediatrician in the Philadelphia area for almost 15 years. He has lectured extensively throughout the country on the value and importance of immunizations. He is a well-respected, national advocate for immunization initiatives.

Andrew Macknight

Mr. Macknight is Executive Director of Vaccine Policy at GlaxoSmithKline. He is responsible for coordinating immunization policy for GlaxoSmithKline's vaccines business in the U.S. and for business planning and delivery of vaccines to the Centers for Disease Control. He is currently leading policy for the launch of several GSK vaccines in development, including vaccines against cervical cancer and rotavirus. A native of Scotland, Mr. Macknight has worked for 18 years in the areas of strategic product development and commercialization, with experience in both the biotechnology and pharmaceutical industries.

Robert Mittman, MS, MPP (Moderator)

Mr. Mittman is founder of Facilitation, Foresight, Strategy. An experienced moderator, Mr. Mittman brings a multidisciplinary perspective to emerging technology and health care forecasting and planning. Mr. Mittman specializes in developing innovative approaches to modeling and forecasting under conditions of little or conflicting data. He is co-author of *The Future of the Internet in Health Care: A Five-Year Forecast.* He was also a contributing author of IFTF's annual *Health Care Outlook* report and of *The Future of American Health Care, Vol. IV, Transforming the System: Building a New Structure for a New Century*.

Walter Orenstein, MD

Dr. Orenstein is the former Director of the National Immunization Program at the Centers for Disease Control and Prevention, a $1.6 billion effort with more than 450 staff, dedicated to reducing vaccine preventable disease burdens around the world. Currently, Dr. Orenstein is Director of the Emory Program for Vaccine Policy and Development and Associate Director of the Emory Vaccine Center. During Dr. Orenstein's tenure at the National Immunization Program, he led successful efforts to combat and markedly reduce the occurrence of common childhood diseases. He also led the effort to implement the Vaccines for Children Program and fostered development of a major effort to address vaccine safety concerns, including overseeing the Vaccine Adverse Event Reporting System (VAERS). He is a fellow of the American Academy of Pediatrics, the Infectious Diseases Society of America, and the Pediatric Infectious Diseases Society and has served on the Council of the Pediatric Infectious Diseases Society.

Debbie Saslow, PhD

Dr. Saslow is the national director of breast and gynecologic cancer in the Department of Cancer Control Sciences at the American Cancer Society. She is responsible for ensuring the scientific integrity of the Society's breast and gynecologic cancer policies, materials, programs and communications. Dr. Saslow directed and oversaw the development and publishing of evidence-based consensus screening guidelines for breast, cervical and endometrial cancers. She has worked extensively to build and maintain collaborative relationships with organizations across the public, private, and not-for-profit sectors and to achieve consensus on many complex issues in her field. She holds a PhD degree in molecular and human genetics from Yale University and received her Bachelor of Science degree from Brown University. Prior to joining the American Cancer Society in 1997, Dr. Saslow coordinated the work of the President's National Action Plan on Breast Cancer within the U.S. Department of Health and Human Services.

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[58] Due to the failure of targeting high-risk individuals only (hepatitis B) universal vaccination for a certain age and gender is considered to be the most efficient and effective way to disseminate the HPV vaccine. Source: Jain N, Yusuf H, Wortley PM, Euler GL, Walton S, Stokley S. Factors associated with receiving hepatitis B vaccination among high-risk adults in the United States: an analysis of the National Health Interview Survey, 2000. *Fam Med*. 2004;36:480-486.

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[61] Merck's list price for Gardasil® is $360 for the full three dose series or $120 per dose. Source: Merck. Product News. *FDA approves Merck's Gardasil®, the world's first and only cervical cancer vaccine*. Available at: http://www.merck.com/newsroom/press_releases/product/2006_0608.html. Accessed July 7, 2006.

[62] Note, a study by Elbasha & Dasbach (Merck), estimated cost-effectiveness to be $728, but this assessment included the value of a vaccine that also protects against HPV types 6 and 11 which are known to cause 90 percent of genital warts.

[63] According to the Harvard Center of Risk Analysis, "There is no consensus on the cost per QALY that represents acceptable value for money. According to Associate Professor Peter Neumann, values ranging from $50,000 to $100,000 are sometimes used as a benchmark in the United States. Such values are relative, however: Cost-effectiveness is just one of many factors in any assessment of a treatment or preventive measure, Neumann says. Also important are whether effective alternatives exist, the total health budget, and society's moral and ethical values." Source: Harvard Public Health Review. *What price health? Cost-effectiveness analysis can help society get the biggest bang for the buck*. Available at: http://www.hsph.harvard.edu/review/review_fall_04/risk_whatprice.html. Accessed July 7, 2006.

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[65] The range of values for cost-effectiveness, as measured in cost per quality-adjusted life years gained, ranges from $26,000 to $66,000.

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[71] ACIP recommendations, and in particular the language used in the recommendations, will greatly impact clinician acceptance of the vaccine as well as coverage. In addition to providing recommendations, the ACIP also has the authority to vote for the inclusion of new vaccines into the VFC program, which provides vaccines to 42 percent of America's children. Private plans also use ACIP recommendations—in a survey by America's Health Insurance Plans, over 91 percent of health insurance plans indicated that the ACIP recommendations are used to determine vaccine coverage. Once recommended by the ACIP,

recommendations from professional societies typically follow. Once the various recommendations are harmonized, clinicians are signaled to begin recommending the vaccine to patients.
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[73] While there is limited estimates regarding immunization rates among young adults, immunizations for older adults have long be less than ideal. Influenza, pneumococcal disease, and hepatitis B continue to cause between 50,000 and 90,000 deaths a year in the United States, despite the availability of safe and effective vaccines against these diseases. Source: Reid KC, Grizzard TA, Poland GA. Adult immunizations: recommendations for practice. *Mayo Clin Proc. 1999;74:377-384.*
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[82] A survey by America's Health Insurance Plans (AHIP) shows that of the most popular plans offered by private insurers, coverage for adolescent and adult vaccines ranged from 86.5 – 90 percent, depending on the vaccine. Estimates from an IOM study are not as generous—suggesting that as many as 15 percent of children and more than 30 percent of adults have private insurance that does not provide vaccine coverage. Source: McPhillips-Tangum C, Rehm B, Hilton O. Immunization practices and policies. *AHIP Coverage*. Jan-Feb 2006.
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[84] According to 2004 Biologics Surveillance Data, 40 percent of childhood vaccine doses come from VFC, 45 percent from the private sector, 8 percent from the Section 317 funds, and 7 percent from state funds. NEHI is using these numbers as a proxy for the percentage of children under the age of 19 who receive their vaccines from the various funding sources.
[85] U.S. Department of Health and Human Services. National Vaccine Advisory Committee. November 29-30, 2005. *Newly approved vaccines and financing*. Available at: http://www.hhs.gov/nvpo/nvac/nov05.html. Accessed on June 26, 2005.
[86] To illustrate the inadequacy of current levels of Section 317 funding, NEHI has projected the cost of immunizing the entire adolescent population for which the HPV will be recommended and covered by the VFC—ages 11 to 18. Note, the vaccine is covered by the VFC for ages 9-10, but this population is not expected to be either the primary or catch-up population. To meet an ideal immunization rate of 80 percent, 12.5 million female adolescents must be vaccinated. NEHI conservatively estimated that this goal would be reached over the course of 5 years, with 15 percent adoption within the first year. This analysis is for the gap in funding for the HPV vaccine only. To incorporate other newly recommended vaccines, such as rotavirus, the gap in funding would be much larger. For full details of the analysis, please contact the New England Healthcare Institute.
[87] Ibid. Note: The House Appropriations Committee allocated an increase in the FY 2007 Labor, Health, Human Services and Education bill for Section 317 and issued a directive for the CDC to report how much funding is needed to cover the cost of new vaccines.
[88] Indystar.com. M-Plan, Wellpoint to cover vaccine. Available at: http://www.indystar.com/apps/pbcs.dll/article?AID=/20060701/BUSINESS/607010391/-1/ZONES04. Accessed July 10, 2006.
[89] Berman S. Do we need a structural engineer to redesign our vaccine infrastructure? *Pediatrics*. 2003 Sep;112(3 Pt 1):671-672.
[90] Expert Interview.
[91] Studies indicate that most adolescents have a usual source of medical care that they utilize at least once per year. However, it is less clear what percentage of adolescents receives preventive care (well-visits) within a medical home—estimates have ranged from 36 to 89 percent according to a summary of the literature developed by Cynthia Rand. A 1997 Commonwealth Fund Survey which uses self-reported data found that 89 percent of 5th-8th graders reported having a well-visit, however a study using HEDIS data found that 34 percent of adolescents overall have annual preventive visits (Source: McInerny TK, Cull WL, Yudkowsky BK. Physician reimbursement levels and adherence to American Academy of Pediatrics well-visit and immunization recommendations. *Pediatrics.* 2005; 115(4):833-838.) According to a poster sessions presented at the 2006 Pediatric Academic Societies' Annual Meeting, less than half of females ages 11-12 receive one or more primary health care visits per year. (Source: Adolescent healthcare utilization across the U.S.: who may be reached for immunization. Available at: http://www.abstracts2view.com/pas/view.php?nu=PAS6L1_2171. Accessed July 6, 2006.)

[92] Historically, medical home has been determined by the presence of a usual or primary source of care, such as a pediatrician or a family physician. In 2002, the American Academy of Pediatrics (AAP) described the medical home as "health care delivered or directed by well-trained physicians who provide primary preventive, acute, and chronic condition care and care that is 1) accessible, 2) continuous, 3) comprehensive, 4) family-centered, 5) compassionate, 6) culturally effective, and 7) coordinated with specialized services provided outside the primary care setting. It should be delivered or directed by well-trained physicians who provide primary care and help to manage and facilitate essentially all aspects of pediatric care. The physicians should be known to the child and family and should be able to develop a partnership of mutual responsibility and trust." Source: American Academy of Pediatrics, Medical Home Initiative for Children with Special Needs Project Advisory Committee. The medical home. *Pediatrics*. 2002;110:184-186.
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[94] The dosing schedule for Gardasil® is 0, 2, 6 months. Cervarix® is likely to have a 0, 1, 6 month schedule. Source: Merck Product News. *FDA approves Merck's Gardasil ®, the world's first and only cervical cancer vaccine*. Available at: http://www.merck.com/newsroom/press_releases/product/2006_0608.html. Accessed July 7, 2006.
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[100] Phone interview CDC.
[101] Centers for Disease Control and Prevention. Immunization information system progress-United States, 2004. *MMWR Recomm Rep*. 2005;54(45):1156-7.
[102] Oster NV, McPhillips-Tangum CA, Averhoff F, Howell K. Barriers to adolescent immunization: a survey of family physicians and pediatricians. *J Am Board Fam Pract*. 2005;18(1):13-19.
[103] Over 85 percent of physicians in a recent study conducted by the American College of Physicians felt that they are inadequately reimbursed for the administration of the vaccine. Source: *American College of Physicians Statement to the National Vaccine Advisory Committee (NVAC) on reimbursement for vaccine administrations*. Available at: http://news.acponline.org/hpp/reimbursement.htm. Accessed July 6, 2006.
[104] According to a presentation by Dr. Joel F. Bradley of the American Academy of Pediatrics at the June 6, 2006 National Vaccine Advisory Committee, CMS has finally published fully valued RBRVS (Resource Based Relative Value Scale) for immunizations, which payers use to determine reimbursement rates for physician service. This change should greatly improve clinician reimbursement for providing immunizations.
[105] AHIP's survey did indicate that 57 percent of plans do not provide office visit reimbursement to clinician when the only service performed is routine immunization, although 75 percent reported paying for the vaccine and the administration of the vaccine on a fee-for-service basis. Source: Phillips-Tangum C, Rehm B, Hilton O. Immunization practices and policies. *AHIP Coverage*. Jan-Feb 2006.
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including plans pre-empted under the Employment Retirement Income Security Act (ERISA). Senate Bill 2444. Washington, DC: Government Printing Office; 2000.
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