Two Roads to Providing the HPV Vaccine: 
a United States-United Kingdom Comparative Analysis of 
Adopting and Allocating a Preventive Therapy

By

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Abstract

Vaccinating populations against a common cancer seems like a public health and health outcomes miracle, but that is the hope of those who have worked to develop and disseminate a human papilloma virus (HPV) vaccine. The United States Food and Drug Administration (FDA) and the United Kingdom Joint Committee on Vaccination and Immunisation (JCVI) approved a new HPV vaccine, Gardasil, in 2006 and 2007 respectively. The vaccine's approval is a substantial and still unfolding event in both systems' health services, health care quality, and public health outcomes arenas. The vaccine has the potential to cost and possibly to save billions of health care dollars, to save millions of people from contracting sexually transmitted HPV infections, and to prevent thousands of women from developing cervical cancer annually. This research compares and contrasts the response to the new HPV vaccine by the health systems and political environments in the United States and the United Kingdom.
Acknowledgements

I especially want to acknowledge and thank my advisor Dr. Sue Tolleson-Rinehart for her outstanding guidance and encouragement in this research.

I also wish to thank and acknowledge Dr. Jon Oberlander for his insights and review of my research as a member of my master's paper committee.

To attain the latest perspectives on the dynamic issues surrounding the new HPV vaccine, I interviewed key players in the HPV vaccine discussion in the United States and the United Kingdom.

In the US I interviewed Sheila Leatherman, Alan Cross, Janet Gilsdorf, Lauri Markowitz, Lisa Goldstein, and Amy Allina.

In London I interviewed Andrew Hall, David Hicks, Tony Kerridge, and Sue Baldock.

I am extremely grateful to these top authorities in their professional capacity as physicians, government officers, and health care political analysts for sharing their valuable time, knowledge, critical insights and perspectives on the health care systems and the acceptance of the new HPV vaccines in their respective countries.
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Introduction: Two Roads Diverged in a Wood...

The United States and United Kingdom, despite the complexity and sophistication of their health care systems, can still find themselves in the woods of confusion about the best roads toward better health for their populations. Vaccinating populations against one cause of a common cancer seems like a public health and health outcomes miracle – a sure road through the woods – to many. Such a strategy is precisely the hope of those who have worked to develop and disseminate a human papilloma virus (HPV) vaccine. The United States Food and Drug Administration (FDA) and the United Kingdom Joint Committee on Vaccination and Immunisation (JCVI) approved a new HPV vaccine, Gardasil, in 2006 and 2007 respectively. The vaccine's approval is a substantial and still unfolding event in both systems' health services, health care quality, and public health outcomes arenas. The vaccine has the potential to cost and possibly to save billions of health care dollars, to save millions of people from contracting sexually transmitted HPV infections, and to prevent thousands of women from developing cervical cancer annually.

The delivery of HPV vaccination will take place in health service delivery systems that differ in substantial ways, despite the many similarities between the United States (US) and the United Kingdom (UK). In the course of the last 100 years, the US and UK have taken very different paths to the creation of their present day health systems. In the UK, decisive governmental actions following World War II led to the creation of the National Health Service (NHS), setting the stage for the current system of care. The national government finances all care provided by the NHS through taxation. Over the past century the US system has persisted in a public-private hybrid, despite several notable attempts at health care policy reform in early 1930s, mid-1960s, and early 1990s. The US hybrid system is financed by employer-based and individual private insurance institutions along with tax-payer provided public assistance to the elderly and a limited number of other groups in the form of Medicare, to the poor individuals and
families via Medicaid, and to the poor children with State Children's Health Insurance Program (SCHIP); with the small remainder financed via eleemosynary institutions or through direct out-of-pocket payments from those who receive care.

The paths the US and UK took to their health care systems also inevitably influenced system dynamics. The NHS's organization enhances its ability to accomplish system-wide reform, quality initiatives, and evaluation of effectiveness and safety. The US system, although it has attempted in recent years to craft broadly embraced reform efforts, lacks the UK's ability to impose system-wide reform from above, with one exception: the Centers for Medicare and Medicaid Services (CMS) is such a larger purchaser of care, through its financing of Medicare, that it is often seen as a desirable vehicle to drive reform. Medicare recipients, however, are not the targets of HPV vaccination programs, meaning that Medicare will likely not contribute to the shaping of American HPV vaccine policy (Medicaid's constraints, as a federal-state program, mean that its influence on policy will vary from state to state, as noted below).

Regulation of drugs, biologics – including vaccines – food, medical devices, and certain other products has its original motivation in the US in concerns about the increasing distribution of adulterated products, often leading to deaths, and a desire to protect the public from poor quality and false claims made for them. Particularly appropriate for the present work, a diphtheria vaccine tainted with tetanus that killed a number of children sent safety concerns to the head of the public agenda. Passage of the Pure Food and Drugs Act of 1906, which gave the government control over drug labeling, began a century's worth of supervision and management of drugs, devices, and biologics.² In 1927 the "Bureau of Chemistry" was reorganized and regulatory functions were allocated to the "Food, Drug, and Insecticide Administration," shortened to "Food and Drug Administration" (FDA) under an agricultural appropriations act in 1930. This legislation was followed by the Food, Drug, and Cosmetic Act in 1938 that extended control over advertising and labeling and required proof that drugs were safe, and the 1962 Amendments to this act, adding proof of efficacy to proof of safety as a
another criterion for drug and vaccine approvals. Medical devices came under FDA control in 1976 with the passage of Medical Device Amendments.3

In the US, some regulation of therapeutic products had begun before the medical profession had developed much of its present day autonomy and authority. In contrast, when the NHS was established in Britain in 1948, its clinical standards were those of individual clinicians and their professional organizations. The autonomy and authority of physicians in the UK were established before the Beveridge Report produced the HNHS; if the NHS had tried to challenge the traditional freedom of clinicians, the medical profession might have walked away from the fledgling national service. Subsequently, attitudes in the UK have changed. Medical practice “based on evidence, rather than on anecdote and opinion,” gained acceptance.4 Studies during the 1990s revealed that the results of clinical research were poorly incorporated into routine care and that inappropriate variations in the standards of clinical practice were common in Britain.4

As part of the 1998 Comprehensive Spending Review of the NHS, officials were asked to look at ways of improving efficiency and effectiveness in the NHS. The report proposed a systematic and national approach to the appraisal and management of new therapies. The White Paper, "The New NHS," announced the establishment of a new National Institute for Clinical Excellence (NICE), with an aim to include guidance on drugs and other technologies. NICE, established in 1999, brought together a number of organizations previously established to work on quality issues in the UK.

These two regulatory climates provide part of the context for approval of the HPV vaccine in the US and UK health care systems. Another feature of the context is the most important reason for developing an HPV vaccine: cervical cancer, its etiology, and its susceptibility to prevention. The next section provides an introduction to the epidemiology of cervical cancer.
The Epidemiology of Cervical Cancer

The etiology of cervical cancer and pre-neoplastic lesions is now accepted to be the HPV. Approximately 100 strains of HPV exist, roughly 20 of which infect the cervix.\(^5\) Approximately 10% to 20% of sexually active adults exhibit molecular evidence of current genital HPV infection, 50% to 75% of which are high risk, oncogenic types. Serological evidence suggests that over 50% of sexually active women have had a previous infection with at least one HPV type. The rate of infection by any HPV type among sexually active young women within three years was found to be 44%.\(^6\) However, most of these infections are transient. Women under 25 to 30 years of age have higher rates of infection although a second peak has been described in postmenopausal women.\(^7\)

Today cervical cancer represents the most common cancer among women worldwide. Globally, cervical cancer has been estimated to account for 2.1% of deaths among women aged 25-64.\(^8\) However, it is much more common in developing countries, where more than 80% of cases occur.\(^7,8\) This disproportionate disease morbidity and mortality in the developing world makes cervical cancer the leading cause of cancer death among these women.\(^10\) In developing countries 83% of cases occur and cervical cancer accounts for 15% of female cancers, with a risk before age 65 of 1.5%. In developed countries, cervical cancer accounts for only 3.6% of new cancers, with a cumulative risk (0 to 64) of 0.8%.\(^7,10\) Ironically, but not surprisingly, given the pharmaeconomics, the HPV vaccine just approved does not protect against the most common oncogenic strains in the developing world.

This pattern of greater burden of disease in the developing than the developed world is relatively recent, however. Before the introduction of screening programs in the 1960s and 1970s, the incidence in most of Europe, North America, and Australia/New Zealand was similar to that of developing countries today.\(^8\) In the US today, an estimated 10,400 new cases of cervical cancer and 3,700 deaths from the disease occur annually, making it the eleventh leading cause of cancer deaths among American women.\(^9\) In the UK, an estimated 2,800 new
cases of cervical cancer and 1,100 deaths occur annually, making it the twelfth most common cancer in women.\(^\text{11}\)

Cervical cancer presents a largely preventable burden of suffering to women in the US and the UK. Many prevention strategies exist in these high resource health environments. Papanicolaou (Pap) smears have been instrumental as a prevention tool against cervical cancer. They have proven to be cost-effective and increase quality adjusted life years.\(^\text{12}\) The research available for Pap smears is extensive and the magnitude of the net benefit of Pap smears is substantial. The new HPV immunization has re-focused this public health and women’s health issue to the forefront of health policy discussions.

The FDA approved Gardasil™, Merck’s quadrivalent HPV vaccine, in June 2006, making it the only FDA-approved vaccine currently available. The vaccine protects against four strains of HPV: 6, 11, 16, and 18. Almost 70% of cervical cancer cases in the developed world and 90% of genital warts cases are linked to these four strains of HPV.\(^\text{13}\)

As I have noted, the problem of cervical cancer is a global health issue, with a disproportionate burden of disease in the developing world. But because Gardasil™ is approved for use and targets the most prevalent oncogeneic strains in the US and the UK, I will focus on strategies for prevention in American and British women. This paper aims to address the political and policy-making implications of HPV immunization adoption and dissemination. I hope to compare and contrast US and UK approaches to the potential role of HPV vaccination in cervical cancer prevention. This paper reviews the different political abilities — by which I mean both structural capacity and ideological feasibility -- of the US and UK health systems. It assesses how political structures affect the making of health care policy. I evaluate the two national regulatory agencies, FDA and NICE/JCVI, comparing their roles and capabilities, approval processes, safety checks, and the effect of direct-to-consumer advertising, as the latter may have its own effect on quality of care and acceptance of approved drugs and/or clinical guidance. With this focus, I hope to offer a better understanding of where the two public health
infrastructures excel or fail in this novel opportunity actually to prevent a cancer through vaccinating a population.

The natural history of cervical cancer

Cervical cancer progresses from a pre-neoplastic condition referred to as cervical intraepithelial neoplasia (CIN). CIN progresses slowly, allowing for early detection and treatment. Not all cases of CIN progress to invasive cervical squamous carcinoma, and some even regress. The two main types of cervical cancer are squamous cell (about 80% of cases), and adenocarcinoma (about 10-20% of cases). The process of cervical carcinogenesis may take from ten to 30 years from HPV infection to progression to invasive cancer, and many HPV infections never cause cancer.5

Three grades of CIN describe the progression of the precursor state. CIN I, a low-grade lesion, represents mild dysplasia, corresponding to flat condylomas. CIN II, a high-grade lesion, represents moderate dysplasia. Finally, CIN III, also a high-grade lesion, represents severe dysplasia and carcinoma in situ.6

The etiology of cervical cancer and pre-neoplastic lesions is now accepted to be the HPV. Approximately 100 strains of HPV exist, roughly twenty of which infect the cervix. HPV subtypes with high risk of malignant transformation of cervical epithelium include types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, and 58. HPV subtypes with low risk of malignant transformation include types 6, 11, 42, 43, and 44.5

HPV is the most common sexually transmitted disease in the US.16 More than 6 million people in this country become infected with HPV every year, and nearly 10,000 women are diagnosed with cervical cancer.15 Approximately 10% to 20% of sexually active adults exhibit molecular evidence of current genital HPV infection, 50% to 75% of which are high risk strains. Serological evidence suggests that over 50% of sexually active women have had a previous infection with at least one HPV type. The rate of infection by any HPV type among
sexually active young women within three years was found to be 44%. However, most of these infections are transient. Women under 25 to 30 years of age have higher rates of infection although a second peak has been described in postmenopausal women.

Cervical cancer represents the most common cancer among women worldwide, with an estimated 500,000 new cases and 260,000 deaths in the year 2005. Cervical cancer is much more common in developing countries, where 83% of cases occur. Rates of cervical cancer vary between countries and also between ethnic populations in the same country.

Worldwide, cervical cancer accounts for 15% of female cancers, with a risk of 1.5% before age 65. In developed countries, cervical cancer accounts for only 3.6% of new cancers, with a cumulative risk (0 to 64) of 0.8%.

The highest incidence rates are observed in sub-Saharan Africa, Melanesia (the islands in the southwestern part of Oceania), Latin America and the Caribbean, south central Asia, and southeast Asia. Incidence rates are now generally low in developed countries, with age standardized rates less than 14.5 per 100,000.

Mortality rates are substantially lower than are incidence rates. Worldwide, the ratio of mortality to incidence is 55%. Survival rates vary between regions. In low-risk regions, outcomes can be quite good. For example, the overall survival rate in the US is 74%, and it is 63% in Europe. Even in developing countries, where many cases present at relatively advanced stages, survival rates are fair. Survival is not the only question, however. Cervical cancer also causes a significant amount of morbidity annually. The thousands of Pap smears in the US and UK lead to many invasive procedures such as colposcopies, cone biopsies, and further surgeries. These procedures carry many risks as well as benefits. The loss of fertility as well as the emotional toll of the experience can be devastating.
Risk Factors

Although HPV infection is the primary etiologic agent involved in the development of cervical cancer, several risk factors exist. These include high parity, tobacco smoking (and, in the developing world, long exposure to wood-burning cooking fires), intercourse at an early age, large number of sexual partners, a history of sexually transmitted infections (STIs), genetic predisposition, maternal DES use, alcohol use (2-4 drinks per week), use of oral contraceptives (particularly greater than 5 years of use), and low socioeconomic status. Immunosuppression has a role as well, possibly acting by interfering with the immune response that the body mounts against the cells that are infected with HPV.

Substantial declines in cervical cancer incidence and mortality are most clearly observed in western countries with well-developed systematic screening programs. Declines are also evident in some developing countries. This trend is particularly striking in China, where the estimated age-standardized incidence rate in 2002 was 6.8, compared with 17.8 in 1985. As a result of these trends, cervical cancer has relinquished its place to breast cancer as the leading cancer in developing countries. Only in sub-Saharan Africa, Central America, south-central Asia, and Melanesia has it remained the most common cancer affecting women.7

US cervical cancer statistics and HPV prevalence. The incidence of cervical cancer in the US has decreased from 14.2/100,000 in 1973 to 7.4/100,000 in 1994 with 14,000 cases and about 4,000 deaths annually.17 In the US today even lower rates are seen. In 2006, an estimated 10,400 new cases of cervical cancer and 3,700 deaths from the disease occur annually. It is the eleventh leading cause of cancer deaths among US women.9

In the US the burden of suffering is largely carried by American Indians, Hispanics, African-Americans, and Asian/Pacific Islanders. The trends of disease also correlate with lower socio-economic status (SES) and lower education level. The peak incidence of disease is in
women aged 40-50 years. Actually, less than 25% of all cervical cancers occur in women 65 or older. However, 40-50% of women who die from cervical cancer are over 65 years of age.\textsuperscript{18}

Data from the National Health and Nutrition Examination Survey (NHANES) of more than 2,000 American women aged 14 to 59 revealed a 26.8% overall HPV prevalence among US girls and women, with increasing prevalence each year for ages 14 to 24 years (44.8% for ages 20-24 years) followed by a gradual decline in prevalence through age 59 years (19.6% for ages 50-59 years).\textsuperscript{19} Although infection with high-risk HPV types is necessary for the development of cervical cancer (detected in 99% of cervical cancers), high-risk types 16 and 18 have a relatively low prevalence (3.4% of all HPV infections), and not all women who are infected with high-risk HPV types will develop cervical cancer.\textsuperscript{19} Approximately 90% of women with new HPV infections clear the infection within 2 years.\textsuperscript{20}

Research estimates that a 26.8% infection prevalence of any strain of HPV in the vaginal tract was equivalent to almost 25 million women.

Of note, HPV prevalence rose during adolescence and peaked among college-age women (20 to 24 years of age), with almost half (44.8%) of women in this age group testing positive for the virus. Overall, the rate of infection of all types of HPV for females aged 14 to 24 was 33.8%, or about 7.5 million young American women. That rate is substantially higher than previous estimates of about 4.6 million HPV infections in this same age group.\textsuperscript{21} An additional important caveat is that because the body’s immune system usually clears HPV from the body within six months, the study results do not reflect a woman’s lifetime risk of ever acquiring the virus.

According to the American Cancer Society (ACS) in the US, 27% of women who have cervical cancer die within five years.\textsuperscript{22}

**UK cervical cancer statistics and HPV prevalence.** In the UK, an estimated 2,800 new cases of cervical cancer and 1,100 deaths occur annually, making it the twelfth most common cancer in women and accounting for about 2% of all female cancers.\textsuperscript{8} The annual
incidence of cervical cancer in 2003 was estimated to be 9.7 per 100,000 population, which corresponds to a mortality rate of 3.9 per 100,000.23

The lifetime risk of developing cervical cancer in the UK is one in 116. In England, 2221 new cases of invasive cervical cancer were diagnosed in 2004. In addition around 200,000 women in England are identified through the cervical screening program as having a precancerous change.24

The HPV prevalence data from the UK are being gathered now by the Health Protection Agency. They plan to test 1000 biopsies, 1000 CIN3 lesions, and 5000 LBC samples for type-specific HPV infections. The Agency also plans to test residual genital samples from 5000 young girls attending Chlamydia screening. These data are expected to be available by the end of 2007.24

Additionally the UK Cancer Research Group plans to type 1000 abnormal cytology samples from women in their 20’s referred for colposcopy. These data will be available mid-2007.24

Prevention Strategies

Numerous prevention strategies exist for reducing the burden of cervical cancer including public education, counseling and lifestyle change, testing for HPV DNA, screening with Pap smears, and most recently immunization against HPV. No one age group can be targeted with a single prevention strategy due to the long latency period between HPV infection and development of cervical cancer.

Educating the public that cervical cancer is caused by a virus and that this virus is sexually transmitted is necessary, and it can be reinforced during other educational and counseling sessions, especially those in which lifestyle choices are discussed with adolescents. "Protective" lifestyle modifications include abstaining from or delaying sexual intercourse during adolescence, reducing the number of sexual partners, using condoms, and refraining from
smoking. This kind of lifestyle choice counseling, however, is both time-consuming for providers and emotionally sensitive for patients. Unfortunately, screening women for HPV infection through DNA analysis is not cost effective for the present, but it may be useful in women with repeated Pap smears showing atypical squamous cells of uncertain significance (ASCUS). DNA testing is useful for detecting high risk HPV strains, so women with ASCUS results can be followed more closely.

Currently, the most common screening tool in the US and UK is the Pap test, which is used to screen the asymptomatic population. The HPV vaccine's introduction will not replace Pap smears completely, or even partially, for the foreseeable future.

**Pap smear screening practices and guidelines**

The decreased incidence and mortality from cervical cancer in the US and UK in recent decades are largely attributed to the success of widespread Pap smear screening programs. Many studies report fairly divergent numbers for sensitivity and specificity of Pap smears, despite our assumption that it is the screening program that has caused the retreat of cervical cancer in the two places. A systematic review of 12 studies with the least biased estimates reported values ranging from 30 to 87% for sensitivity and 86 to 100% for specificity when low grade squamous intraepithelial lesions or above was used as the threshold (i.e. the point at which the test will be considered to be “positive”) for detection of CIN I or greater in a screening population, a reference-standard threshold. In practice, ASCUS is often used as the test threshold and CIN I is often used as the reference threshold. Moreover, accuracy is greatly affected by the adequacy of the sample, how it is fixed and stained, and the abilities of the cytotechnologist. Efforts to improve the test’s accuracy include liquid-based or “thin prep” cytology and computer-assisted cytology, both of which are still being assessed. However, despite these variations in accuracy, the research and clinical communities generally agree that high-quality Pap smears are very specific but that their sensitivities are variable.
The efficacy and cost-effectiveness of Pap smears is well documented. The establishment of a population-based screening program with ideal screening intervals involves considerable infrastructure, workforce, and equipment costs. Benefits of screening have been demonstrated for women having tests every 10 years or even once during a lifetime.  

The first evidence of the effectiveness of screening came from the Nordic countries. In five countries, the cumulative mortality rates between 1965 and 1982 were studied in relation to the extent of the screening program. In Iceland, where the nationwide program had the widest target age range, the fall in mortality was greatest (80%). Finland and Sweden had nationwide programs also; in these countries the mortality fell by 50% and 34%, respectively. In Denmark, where about 40% of the population was covered by organized programs, the overall mortality dropped by 25%, but in Norway, with only 5% of the population covered by organized screening, the mortality fell by only 10%.  

The potential harms of screening Pap smears include false negative and false positive results. The false negative rate is approximately 20% per smear, which can lead to a false sense of security and allow pre-neoplastic lesions to advance undetected. The false positive rate is approximately 12%, and can lead to increased procedures, including repeat Pap tests and biopsies, and psychological distress.  

With Pap smears, it is not always possible to differentiate among rapidly growing cancers that arise in the screening intervals, cancers that were missed in the previous screen, or in women who have not been screened recently at all, although it is speculated that most cases are due to the latter two circumstances. This worry has raised the question of the appropriateness of the process of cervical cytology sampling and interpretation as a screening test.  

In the US, www.guidelines.gov points to three main organizations that have established guidelines for screening Pap smears. All three sets of guidelines were developed through systematic evidence review. Additionally, the ACS employed a consensus process.
The ACS recommends that initial cervical cancer screening be performed annually if conventional Pap smears are used and every two years with liquid based cytology (LBC) tests until age 30. The screening interval can then be increased to every two to three years in women with three or more consecutive normal cytology results who are (30 years or older) ≥ 30 years old. Combined testing was not yet approved at the time these guidelines were established in 2002. The ACS guidelines state that women age 70 or older may elect to stop cervical cancer screening if they have had three consecutive satisfactory, normal/negative test results and no abnormal test results within the prior 10 years.\(^2^8\)

The American College of Obstetricians and Gynecologists (ACOG) recommends annual screening for women younger than age 30 regardless of testing method (conventional Pap or LBC). Women aged 30 and over who have had three negative smears, no history of CIN II/III, and are not immunocompromised or DES exposed in-utero may extend the interval between tests to two or three years; however, annual cervical cytology alone (not combined with HPV DNA testing) is also acceptable. Women aged 30 and over may also consider the option of a combined cervical cytology and HPV DNA test. Women who test negative by both tests should not be screened more frequently than every three years due to the high associated costs of the double testing and the reassurance due to the low false negative rate of the combined testing. ACOG recommends individualization based upon annual assessment of risk factors and examination (visual inspection of the vulva and vagina and palpation by bimanual and rectovaginal examination). These guidelines were first set forth in 1995, revised in 2003, and again in 2006.\(^2^9\)

In contrast, the US Preventive Services Task Force (USPSTF) recommends the screening interval be extended to every three years in women of any age who have had at least two normal annual Pap smears. The USPSTF has not endorsed use of liquid-based tests or HPV DNA testing because its members feel that there are insufficient data showing superiority of these modalities over conventional Pap smears. The USPSTF stated screening may stop at
age 65 if the woman has had recent normal smears and is not at high risk for cervical cancer. The USPSTF guidelines were first established in 1996 and revised in 2003.30

The guidelines recommend that risk factors for the development of cervical cancer should be assessed on an ongoing basis and taken into consideration when deciding how often and for how long to screen older women for the development of cervical cancer. Women over the age of 65 to 70 who were exposed in-utero to DES or are immunocompromised should continue to be screened annually. Those who have not had regular cervical cytology screening should undergo evaluation. Women who test positive for HPV DNA or have new sexual partners may also benefit from continued screening. Screening is not indicated in women who have a limited life expectancy or who would be unable to tolerate treatment for cervical cancer.29

If it is certain that consensual or nonconsensual sexual activity has never occurred, the provider and patient may defer initiating cervical cancer screening since such women are at extremely low risk of cervical cancer. The upper age limit of 21 years was recommended to ensure screening of women in whom a sexual history was not obtained or who may be reluctant to disclose their sexual activity (i.e. victims of sexual abuse and adolescents). Of note, HPV can also be acquired through same sex contact and non-penetrative sexual contact. Thus, screening should occur within three years of the onset of any sexual contact.

Increasing the frequency of screening (i.e. yearly instead of every two to three years), lowering the threshold for positive results (i.e. ASCUS instead of LSIL), using new technologies (i.e. LBC, HPV DNA testing), and instituting procedures to insure that patients are screened and followed-up after abnormal screening results could help to reduce the number of screening failures. However, the cost of these interventions, the increased number of women who will be referred for unnecessary procedures, and complications from these treatments need to be balanced against potential benefits. Unfortunately, current time interval guidelines are not followed by many clinicians who continue to screen annually even when a patient has had three consecutive normal Pap smears.26 As discussed above, this practice is not cost-effective. On a
global scale, screening women who have not undergone recent Pap smears appears to be the most important factor in reducing worldwide cervical cancer mortality.\textsuperscript{12}

In the UK, until the 1980s, cervical cancer screening was not applied in a systematic fashion.\textsuperscript{31} Recently, as the discussion below makes clear, the existence of NICE and its capacity to evaluate the cost and effectiveness of care mean that we have a much better idea of the performance of Pap smear technologies and programs. The NHS Cervical Screening Program (NHSCSP) began in 1988, screening women aged 20-64 years at three to five-yearly intervals. Approximately 3.9 million are tested in the UK each year, equating to coverage of 71.2\% for three-yearly screening and 81.6\% for five-yearly screening in 2001-02.\textsuperscript{32}

The UK screened with conventional cytology until 2003, when NICE recognized that liquid based testing was as good as the conventional smear test and when their evaluation concluded LBC is cost-effective.\textsuperscript{32,33} The data indicated that there is little difference in average smear taker consultation times between LBC and conventional cytology.\textsuperscript{34} In the US the two technologies used in their pilot test have FDA approval as better than the conventional smear test.\textsuperscript{35}

NICE conducted research that calculated and compared the significant variables in converting to LBC screening in a 322 page document reviewing this decision. Their study compared: administration costs, inadequate slide counts, economies of scale of implementation, labor costs involved, technology costs involved, smear reading time, worst-case scenario costs, and best-case scenario costs.\textsuperscript{35} It is estimated that converting to LBC will cost £10 million additionally. But the reduction in the inadequate rate will reduce the overall costs of screening as fewer smears have to be taken, prepared and read.\textsuperscript{34}

The newer recommendation has changed the age of first screening from 20 to 25. Now, all women between the ages of 25 and 64 are eligible for a free cervical screening test every three to five years. In the light of evidence published in 2003 the NHS Cervical Screening
Program now offers screening at different intervals depending on age. This means that women are provided with a more targeted and effective screening program.\textsuperscript{36}

The new intervals are shown in the table below:

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Frequency of screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>First invitation</td>
</tr>
<tr>
<td>25 - 49</td>
<td>3 yearly</td>
</tr>
<tr>
<td>50 - 64</td>
<td>5 yearly</td>
</tr>
<tr>
<td>65+</td>
<td>Only screen those who have not been screened since age 50 or have had recent abnormal tests\textsuperscript{36}</td>
</tr>
</tbody>
</table>

NICE investigators concluded that cervical cancer is rare in women under 20. Teenagers' bodies, particularly the cervix, are still developing, which means young women may get an abnormal smear result when there is nothing wrong. This practice could lead to unnecessary treatment so screening young women might do more harm than good.\textsuperscript{36}

Under the age of 25 years, invasive cancer is also extremely rare, but changes in the cervix are common. Although lesions treated in very young women may prevent cancers from developing many years later, the evidence suggests that screening could start at age 25. Lesions that are destined to progress will still be screen-detectable and those that would regress will no longer be a source of anxiety. Younger women will not have to undergo unnecessary investigations and treatments.\textsuperscript{36}

British women aged 65 and over who have had three consecutive negative smears are taken out of the screening system. The natural history and progression of cervical cancer means it is highly unlikely that such women will go on to develop the disease. Women aged 65
and over who have never had a smear are entitled to a test. Additionally, if a woman has never been sexually active, then the research evidence shows that her chance of developing cervical cancer is very low. The NHSCSP does not say "no risk," only very low risk. In these circumstances, a woman might choose to decline the invitation for cervical screening on this occasion.  

Implementing and paying for Pap smear programs

Annually in the US, 50 million women undergo screening; about 3.5 million (7%) will be referred for further evaluation. Of these, more than 2 million will be referred for further evaluation of ASCUS. About 12,000 cases of invasive cervical cancer were expected in 2006. Therefore, Pap test screening results in a large number of colposcopies for benign conditions. Strategies to improve the specificity of the cervical cytopathology test are being evaluated by the ASCUS/LSIL Triage Study (ALTS).  

The cost-effectiveness of screening with Pap tests differ significantly when the time interval between tests is changed. For women aged 30 to 44 years of age with no prior tests, incremental cost-effectiveness ratios range from $20,533 for screening triennially (compared with no further screening) to $331,837 for screening annually (compared with biannual screening) per life-year saved. It has been demonstrated that as the number of prior normal Pap test increases, the costs per life-year saved increase substantially. Therefore, health care resources should be prioritized for screening those who have never been or are rarely screened.  

A search of PubMed using keywords "Pap smear, implementation, and frequency" yielded surprisingly few studies examining the degree of implementation of screening Pap smears. The largest study was conducted by the National Center for Health Statistics and employed the National Health Interview Survey, a cross-sectional population-based telephone
survey. Participants were US women age 21 and older who denied a history of cancer (N=16,467).³⁷

Results showed that the vast majority, 93%, of American women report having had at least one Pap smear in their lifetime. Among women with no history of abnormal smears, 55% undergo Pap smear screening annually, 17% report a 2-year screening interval, 16% report being screened every 3 years, and 11% are not being screened regularly. Even the very elderly report frequent screening—38% of women age 75 to 84 and 20% of women age 85 and older reported annual Pap smears. Overall, 20% of women reported having had at least one abnormal Pap smear. Among these women, rates of frequent Pap smear screening are considerably higher—80% undergo annual screening, with only a modest decline in screening frequency with increasing age.³⁷

In the UK, cervical screening combined with the cost of treating cervical abnormalities has been estimated to cost around £157 million a year in England alone.²³ Primary Care Trusts commission cervical screening from the overall allocation they receive from the Department of Health.³⁸

The updated estimate of the cost per smear is higher in the UK, for all the different LBC technologies ranging from £2.37 to £4.26 more than the conventional smear. Nationally, the additional cost of LBC is estimated at between £2.5 and £9.8 million per year.³⁵ The cost effectiveness results indicate that the incremental cost per life year gained of LBC compared to conventional at baseline range from £2,020-£7,900 per life year gained. However, we can still conclude that LBC is a cost effective technology compared to conventional cytology, assuming that the maximum willingness to pay per life-year gained is in the region of £25,000-£30,000.³³

Over the last ten years the percentage of eligible women who have been screened at least once in the previous five years has been declining slightly, to 79.5% in 2006 compared with 80.3% last year and 82% in 1996.³⁸ In 2006, 3.6 million women of all ages were screened, the majority after a formal invitation from the screening program, a similar amount to 2004/05.
While the number of women invited (25-64) has dropped from 4.15 to 4.06 million in the last year, a decrease of 2.2%, the numbers of women screened has risen from 3.28 to 3.36 million, an increase of 2.4%. The percentage of inadequate samples has fallen from just over 9% over the last few years, to the lowest figure recorded: 7.2%. The introduction of LBC sampling is probably the cause of the declining rate of inadequate samples. No other nationally supported screening program is as large as the NHSCSP, nor does any have as high a coverage rate.

The Human Papillomavirus Vaccine

The FDA approved Merck’s Gardasil™, the first HPV vaccine to receive approval, in June 2006. (It was also approved in the European Union before it received approval in the UK). On August 8, 2006, ACOG released its recommendations regarding the use of the HPV vaccine. ACOG recommends that HPV vaccination be offered to all girls and women 9 to 26 years old. Like the Advisory Committee of Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC), ACOG emphasizes that the vaccine is most effective when administered before the onset of sexual activity (i.e. before exposure to the virus) and recommends targeting 11 to 12 year old girls. They additionally stated the largest burden of disease caused by HPV is cervical cancer, a disease of women, and therefore immunization efforts on girls should be the focus. The vaccine is currently not approved for use in boys, and whether boys should be vaccinated, and prevented from spreading the virus, is a significant question, but one that cannot be addressed fully here.

The British NHS and JCVI have not released guidelines, but the UK Department of Health (equivalent to the Department of Health and Human Services in its role as the umbrella agency controlling the NHS) preliminarily announced June 20, 2007 that they plan to make the vaccine available through the NHS in 2008.

GlaxoSmithKline’s (GSK’s) candidate HPV vaccine, Cervarix, was submitted to the FDA and the European Union for potential approval in April 2007 but has not yet received approval.
Cervarix is bivalent, protecting against HPV strains 16 and 18. Researchers in a 2006 study published in the online edition of the *Lancet* also found that Cervarix prevented infection with HPV strains 31 and 45, which together with strains 16 and 18 cause more than 80% of cervical cancer cases. Their research has demonstrated sustained efficacy up to five years against HPV 16 and 18 infections. Of note, Cervarix will not protect against the two strains responsible for genital warts, HPV 6 and 11.

Merck’s vaccine Gardasil took more than twenty years to develop and, as is common with vaccines, is reported to be complex to manufacture. Gardasil is a non-infectious recombinant vaccine, prepared from the highly purified recombinant virus-like particles (VLP) of the major capsid protein (the protein shell of the virus) L1 of HPV types 6, 11, 16, and 18. The key achievements in the pre-clinical development include the stabilization of the VLP antigens (proteins) used that are produced by expressing the type-specific major capsid protein, in yeast. The expression of HPV VLP L1 proteins in yeast cells with substantial yield has considerably benefited both clinical studies and the manufacturing of HPV vaccine for commercial use as it offers the advantages of being cost-effective and easily adaptable to large-scale fermentation. The major challenge of developing HPV vaccine dosage form was the preparation of aqueous/liquid HPV VLP solutions that are stable under a variety of purification, processing, and storage conditions.

The vaccine is administered in three doses at zero, two, and six months intervals. It is unknown whether women will need a booster and if so, at what time interval following the initial dose. The three-dose vaccine costs $120 per injection, $360 for the entire series. In the UK, the vaccine can be purchased privately now for £400-450. In 2008, when the NHS plans to begin distributing the vaccine, its cost to the NHS will be £300 per full course, but it will be free at point of delivery to the individual recipients. The vaccine protects against four strains of HPV: 6, 11, 16, and 18. Almost 70% of cervical cancer cases and 90% of genital warts cases are
linked to these four strains of HPV.\textsuperscript{13} The vaccine studies have established effectiveness and safety, at least in the short-term.\textsuperscript{43}

The magnitude of the net benefit of HPV vaccination has not yet been demonstrated on a large scale. The limited research available on the HPV vaccine is promising, and the net benefit will depend in part on the scale of implementation. Studies investigating the effects of HPV vaccination and its implications for screening Pap smear programs are underway. These studies are attempting to address the potential effects of the vaccine on screening. For example, if a population is vaccinated, can a national recommendation of increased intervals between screenings detect the majority of cancers? The results may have a significant public health consequence given the large amount of resources devoted to prevention and treatment of cervical cancer.

No cost-effectiveness analyses of Gardasil\textsuperscript{TM} are available yet, but projected costs and benefits have been estimated. The CDC has concluded that a vaccine with a 75\% probability of immunity against high-risk HPV infection would result in a life-expectancy gain of 2.8 days or 4.0 quality-adjusted life days at a cost of $246 relative to current practice (incremental cost effectiveness of $22,755/quality-adjusted life year [QALY]). If all 12-year-old girls currently living in the US were vaccinated, more than 1,300 deaths from cervical cancer would be averted during their lifetimes. Vaccination of girls against high-risk HPV is relatively cost-effective even when vaccine efficacy is low. If the vaccine efficacy rate is 35\%, the cost-effectiveness increases to $52,398/QALY. Although gains in life expectancy may be modest at the individual level, population benefits are substantial according to the CDC's sub-committee who reviewed the vaccine's scientific and public health merit.\textsuperscript{39,44} The British JCVI came to the same conclusion with its modeling that also suggested substantial public health benefit in vaccination on a population scale.
The ethics of vaccinating against a sexually transmitted virus

Because the majority of invasive cervical cancers can be attributed to infection with a subset of HPV types, a prophylactic vaccine to prevent infection with one or more types has the potential substantially to reduce the incidence of cervical cancer and its precursor lesions. The benefits of vaccination include reduced HPV infection, reduced cervical cancer, possibly a reduced frequency for recommended cervical cytological testing (pap smears), and decreased genital warts. Other benefits include decreases in other anogenital cancers and decreased laryngeal papillomas.43

The vaccine has potential harms, including adverse reactions, and, at this stage, hypothetical apprehension that vaccination will relax vigilance about safer sex practices, as well as concern about decreased adherence to recommended conventional screening, and the potential misconception that HPV vaccination would be protective against other STIs.

Although the HPV vaccine has a low level of local reactions, widespread use might uncover a rare adverse reaction not uncovered in pre-approval trials. The five most frequently reported symptoms after vaccination with the quadrivalent HPV are syncope, pain at injection site, rash, dizziness, and fever. Three cases each of Guillain-Barre and facial palsy have also been reported.39 Perceived protection from vaccination may potentially make women more likely to engage in riskier sexual activity such as increased numbers of partners and decreased use of barrier protection methods. The possible results of such actions include increased unplanned pregnancies, increased abortions, increased rates of other types of HPV, and increased rates of other STIs including HIV.

In the following pages, we will take a closer look at some of the ethical questions surrounding the vaccine, beginning with whether it ought to be mandatory, particularly in terms of administration to girls young enough, presumably, not to have begun sexual activity (since the vaccine is thought to be most effective prior to a woman’s exposure to the virus).
**State Mandates.** Soon after the HPV vaccine was approved by the FDA for use in the US, lawmakers in numerous states began the discussion of mandating vaccination for school entry.\textsuperscript{45} Controversy quickly arose over the fact that the vaccine protects against an STI, not a causally spread infection, and the dispute invoked arguments about whether the government had the right to require such a vaccine to be mandatory for pre-teenage girls.\textsuperscript{13} Conservative religious groups and concerned parents questioned the effect the vaccine could have on their children's future behavior choices.\textsuperscript{45} Ultimately, 25 states proposed legislation to make the vaccine a requirement for school attendance, and an additional 16 states introduced legislation to fund or educate the public about the HPV vaccine.\textsuperscript{46}

This debate attempts to balance herd immunity and population-level public health concerns with personal family beliefs and individual choice.\textsuperscript{45} The ACIP has not issued a public statement about the state mandate subject, except to note that mandates have been effective way of encouraging large scale, population-wide coverage in the past.\textsuperscript{45} If a vaccine is not required by federal law, then policy choices are made by individual state legislatures.\textsuperscript{47} Even without a state mandate law, a state legislature can direct its state's Health Department to authorize mandatory vaccination, and such vaccination would need state financial support.\textsuperscript{46}

Data confirm that mandates requiring vaccination for school entry are a successful and orderly approach to vaccinating a population.\textsuperscript{48,54,84,84} Necessitating HPV vaccination by law is likely to accomplish more extensive protection against HPV than would public education campaigns alone.\textsuperscript{48} Whether the benefit of widespread immunization will outweigh the public's concerns over the vaccine remains to be seen.

**HPV and Women.** The main purpose of the vaccine is to prevent cervical cancer, a disease of women. Classifying this infection solely as a woman's health issue may "distort funding priorities and increase inappropriate gender stereotypes."\textsuperscript{50} Although some current vaccine studies include men, the testing has chiefly been performed on women. However, HPV
is an STI and spread by men and women. Research shows that women whose sexual partners have had more sexual contacts have an elevated risk for cervical cancer. Moreover, a married woman's risk for cancer is directly associated to the number of extramarital affairs performed by her husband.\(^{51}\) Additionally, cervical cancer death affects women at a fairly young age, resulting in the disruption of family life. In light of these facts, one author argues that "both men and women should share the burden of research and the potential benefits of vaccination."\(^{50}\)

A vaccine for an STI aimed only at women may further emphasize the widespread belief that women ought to take sole responsibility for issues related to reproductive health. Research demonstrates that men do not see themselves as being at risk to HPV and therefore do not consider HPV to be a male health issue.\(^{51}\) These results call into question whether HPV vaccines should be tested on men and, if shown to be effective, recommended for men. As one observer comments "This sort of 'gender-neutral' inclusion can emphasize the need for both men and women to share responsibility equally for sexual and reproductive matters, perhaps having more effect on the sociology of STIs than would vaccines alone."\(^{50}\)

If HPV vaccination is successful in men, herd immunity arguments support immunizing men to make the most of the public health benefits of immunization. Until the vaccines are adequately tested in males, recommendations to vaccinate men must be based on other reasons, such as those of fairness or justice (with awareness that such arguments would be undermined by any finding that the vaccine presented sex-specific safety problems for men).

**Barriers to implementation.** Because the vaccine was approved so recently, we have no published studies on HPV immunization programs. However, we know of many potential barriers to success that will have to be addressed in any attempt to implement a new vaccine to adolescents and young adults, particularly when the vaccine confers immunity against an STI. A search of PubMed using keywords "HPV vaccine and implementation" produced several small studies investigating attitudes toward the vaccine and we will turn to a review of them now.
One study examined HPV vaccine acceptance among parents of 10- to 15-year-old adolescents. Five hundred seventy-five parents or guardians completed a 30-question survey about their knowledge of HPV and acceptance of an HPV vaccine. Afterward, subjects read an HPV educational fact sheet and completed a 26-question post-intervention survey. More than 60% of subjects had a general understanding of HPV pre-intervention. Parents opposed to the HPV vaccine were more likely to believe it would promote earlier initiation of intercourse than did parents who were supportive or undecided about vaccination (24%, 9%, and 6%, respectively; \( p = 0.003 \)). Of the subjects initially opposed to or undecided about the HPV vaccine, 37% and 65%, respectively, supported HPV vaccination after an educational intervention. The authors concluded that a brief educational intervention significantly improved parents' acceptance of the HPV vaccine. The negative effect of an HPV vaccine perceived as condoning early initiation of sexual intercourse seems to be minimal.\(^{52}\)

Other barriers must be attacked before we can expect to achieve high immunization rates among adolescents. Promising interventions for improving vaccination rates at the healthcare system level include reducing out-of-pocket costs, expanding access to immunizations, and implementing vaccination programs in schools. Provider-based interventions for improving vaccination rates include regular assessments of immunization rate with feedback to all office personnel, provider reminders, and standing orders. Client recall and reminders, education, and requirements for school entry can assist in increasing community demand for vaccinations in that they motivate parents and adolescents to follow through with immunizations.\(^{53}\)

**Opportunity costs.** How to invest health resources wisely, such that public health benefits are maximized, and opportunity costs are minimized, is a key question in enhancing Pap smear screening methods, HPV DNA testing, and potential vaccine dispersion. Developing public health policy and useful clinical guidelines will require careful deliberation and thought about the incremental benefits, harms, and costs associated with new interventions compared
with existing interventions, both at individual and population levels. As well as an intervention's efficacy, public health decision making requires the consideration of "feasibility, sustainability, and affordability." No individual clinical trial will be able to consider all of these working parts.

From a health economics and health policy perspective, among the most pressing concerns are the escalating costs associated with current screening routines. For example, in the US, more than 6 billion dollars is spent each year on the evaluation and management of low-grade lesions, the majority of which would regress without intervention.

In the US we are confronted with "the challenge of how to ensure that the huge price paid for achieving a few additional hours of life-expectancy gained does not represent the opportunity cost of reducing disparities in screening that would provide far greater public health benefits." As new tools are developed, how do we keep from moving to more and more spending, using more technology, while health outcomes only marginally increase, if at all?

**Current research.** Because the majority of invasive cervical cancers can be attributed to infection with a subset of HPV types, a prophylactic vaccine to prevent infection with one or more types has the potential substantially to reduce the incidence of cervical cancer and its precursor lesions. The benefits of vaccination include reduced HPV infection, reduced cervical cancer, possibly a reduced frequency for recommended cervical cytological testing, and, for the vaccine that contains antigens against HPV types 6 and 11, decreased genital warts. Other benefits are hypothetical, but include decreases in other cancers and, for the vaccine that contains antigens against HPV types 6 and 11, decreased laryngeal papillomas.

Four multinational placebo-controlled studies of Gardasil's efficacy in women between the ages of 16 and 26 showed that in women who had not already been infected with the type of HPV contained in the vaccine, Gardasil was nearly 100% effective in preventing precancerous cervical lesions, precancerous vaginal and vulvar lesions and genital warts caused by infection.
with the HPV types against which the vaccine is directed.\textsuperscript{57-59} It is believed that prevention of cervical precancerous lesions is highly likely to result in the prevention of those cancers.\textsuperscript{60}

Two studies measured the immune response to the vaccine among younger females aged 9-15 years. Their immune response was similar to that found in 16-26 year olds, indicating that the vaccine should have similar effectiveness when used in the younger group.\textsuperscript{60} These studies suggest that the vaccine is safe and immunogenic for girls aged 9 to 15 years for at least a short term. Additionally, in the studies, females with current or past infection with one or more vaccine-related HPV types prior to vaccination were protected from the diseases caused by the other remaining HPV types contained in the vaccine.\textsuperscript{60} For those older than 15 years, the vaccine provides protection for at least 5 years, and follow-up studies to determine whether protection has longer duration are underway now.\textsuperscript{31}

Gardasil is not approved for use in males, but the manufacturer currently has a study underway to see if it is safe and effective for them. Once the study is complete and submitted to the FDA, the agency will review the data and decide whether to approve Gardasil for males.\textsuperscript{60}

More than 10,500 females who received Gardasil were evaluated for adverse reactions. Most reported reactions were not serious and included mild or moderate local reactions, such as pain or tenderness at the site of the injection. It is always possible that unexpected and rare adverse events can occur when a vaccine is used more widely. The manufacturer has committed to FDA to performing additional "phase IV" studies of the safety of Gardasil. In addition, FDA and CDC carefully monitor the safety of approved vaccine through the Vaccine Adverse Event Reporting System (VAERS).\textsuperscript{60}

Cervarix, GSK's bivalent vaccine against HPV types 16 and 18, though not yet approved, also has been shown to be highly immunogenic and safe, with initial studies results similar to those from the quadrivalent vaccine trials over a period, thus far, of up to four and half years of follow-up.\textsuperscript{92}
**Ethical questions surrounding Merck marketing.** Currently, many health services are marketed as if they were any other consumer commodity. Unfortunately, market forces can often be at odds with the demands of quality and equitable health care. The free market profit incentive encourages pharmaceutical companies to pour research and development dollars into the most profitable products rather than the ones with the greatest potential to improve quality of life for patients. Prescription drug manufacturers air direct-to-consumer advertisements (DTCA) in an effort to increase sales just as any business advertises to increase product demand. The money spent on advertising is not inconsequential. In 2005, pharmaceutical manufacturers spent over $4.2 billion on DTCA, and much of that spending was focused on promoting a specific member of a class of equally-effective drugs. DTCA can be a "counterproductive phenomenon" which results in confusion for patients and providers alike.

Anticipating that Merck's competitor would be on the market soon after Gardasil was licensed for use, the company had a strong financial incentive to establish its place in the market. Weeks before the FDA's approval of Gardasil, US consumers were being advised by television advertisements to "tell someone" that cervical cancer is caused by certain types of HPV, that millions of people are already infected with the virus, and that people may have HPV and not know it.

Merck's promotion features tag lines: "Today, you can do more" and "I want to be one less [case of cervical cancer]." Their "Tell Someone" disease awareness campaign was intended to "prime" the US market for Gardasil's approval and following launch—a detail critics of pharmaceutical marketing are quick to point out. However, with such a significant addition to the pharmaceutical market, arguments against direct-to-consumer communications seem far less substantial.

What is strangely and perhaps strategically missing from the otherwise informative "Tell Someone" television advertisement is the key fact that HPV is transmitted sexually. Merck may have its reasons for omitting this fact. It seems like either "a bad case of old habits dying hard—
the pharmaceutical industry is frequently criticized for its 'tell some, but not all' approach to public education or a soft scare tactic." Either way, according to one critic of the vaccine’s advertisements, "Merck should fill in the gaps. The truth is scary enough."

Merck lobbied legislatures to make the vaccine mandatory for school entry until its withdrawal of the campaign when it became controversial. Since the company stands to profit from widespread vaccine administration, it is not appropriate for a company to financially back attempts to persuade states and public policymakers to make HPV vaccinations mandatory, particularly so quickly after product licensure. One policy analyst commented about Merck’s lobbying efforts that "Private wealth should never trump public health."

### Study Design and Methods

The methods undergirding this study’s findings include obtaining and triangulating data from a variety of sources: the published biomedical literature; public records; media accounts; and in-depth interviews with policymakers and other key informants/stakeholders in the US and the UK.

I searched PubMed using the key words "cervical cancer screening, cost-effectiveness, guidelines, HPV vaccine, immunization recommendations AND HPV, FDA regulation, NHS policy, NICE regulation, direct to consumer marketing, JCVI, UK Department of Health." I read all approval documents on file at the FDA and JCVI for the HPV vaccine, and searched media archives such as the on-line archives of the New York Times and Washington Post for the US, and the Times of London for the UK.

I interviewed key elites including policymakers and other elite stakeholders/key informants in the US and UK who have contributed to or are establishing policy for approval (US) or potential approval (UK) of the HPV vaccine. I identified individuals as possible candidates to be interviewed on the basis of their public positions, and sought to interview at
least one representative from each key political decision-making body for health care policy in both the US and the UK. I identified other potential respondents, such as representatives of the American College of Obstetrics and Gynecology and the Royal College of Obstetricians and Gynaecologists (RCOG) on the basis of their role as their Colleges' designated policymakers in this area.

The structured, open-ended interview protocol, approved by the UNC IRB, led to interviews of 20 to 40 minutes; the questions were principally aimed at elucidating the policy process surrounding the delivery of the HPV vaccine. I conducted each interview by phone or in a private office; I took notes and used a digital voice recorder. I asked participants about their role in women's health policy-making and/or drug/vaccine approval, adoption, and dissemination. Participants were free to provide their best professional judgment as well as their own opinions, and the official positions of the government bodies/groups they represent. Appendix 1 contains the list of respondents, with their positions and the date on which I interviewed them.

System-wide Comparisons

Health service in the US is provided by a complex, multi-layered public-private hybrid system connected (sometimes loosely) by certain shared regulatory and payment constraints. The care the US system delivers ranges from superb quality with the use of the latest technology for a large proportion of patients, about 85%, to more doubtful quality, and the range of access is similarly broad, from access to the whole panoply of care for the well-insured to very limited access, sometimes only through hospital emergence departments, for many. Current estimates put US healthcare spending at a little more than 15% of the gross domestic product (GDP), the highest rate of spending in the world.

In contrast, the UK's National Health Service provides the vast majority of health care in Great Britain, from the financing of care provided by general practitioners to emergency
departments, from long-term health care to dentistry, to every citizen. This universal care attempts to offer comprehensive medical services that are largely "free at the point of delivery." The NHS was founded in 1948 and has become an integral part of British society, culture, and everyday life. The NHS was once described by Nigel Lawson, former Chancellor of the Exchequer, as "the national religion." Private health care has continued in Britain, paid for largely by private insurance and used by about 12% of the population generally in addition to NHS services by elderly or wealthy citizens.

The NHS infrastructure is subdivided into Strategic Health Authorities (SHAs) that oversee all operations in an area. Originally 28 in number, these have been reduced by 2006 to 10 SHAs with the intention of reducing costs, reducing central control, and fostering greater responsibility for decisions closer to the delivery of services. The SHAs are responsible for strategic supervision of the Primary Care Trusts (PCTs), which administer primary care and public health. Three hundred and two PCTs, which are also being reduced in number by about half, try to provide savings by overseeing Britain's 29,000 general practitioners and 18,000 NHS dentists. In addition, the PCTs commission acute services from other NHS Trusts and the private sector, provide primary care directly in their locations, and oversee primary and secondary prevention, immunizations, and control of epidemics. PCTs are at the center of the NHS and control 80% of the total NHS budget. In addition, the SHAs are responsible for the Hospital Trusts, Ambulance Services Trusts, the Mental Health Services Trusts, and NICE.

The UK and US health systems differ greatly in terms of health care infrastructure, spending, and performance. US health care expenditures are more than twice that of the UK per citizen. The US spends $5,711 per capita on health care, 15% of GDP. The UK spends $2,389 per capita, representing 8.0% of its GDP. Despite spending so much more on health care, the US does not appear to have better health outcomes than does the UK.

The World Health Organization (WHO) report supports the strength of the UK health system relative to the US system. In the recent WHO calculation of health system performance
assessment—a metric combining health attainment, equality of health attainment, responsiveness, and financing—the UK ranks 18th out of 191 member countries, whereas the US, despite its vast overall and per capita expenditure on health, ranks 37th. The UK also ranks higher than the US on all five composite indicators except overall health system responsiveness. According to the WHO analysis, the UK health care system performs better than does the US system with significantly less financial burden. It may, then, be reasonable to look to the successes as well as the weaknesses of the British NHS as a comparator for US reform initiatives.

A major challenge to reform of the US health system is its lack of a unified national structure through which public policies are framed and disseminated and care is delivered. It is a “leaderless” system. In contrast, the British NHS assumes responsibility for national health policy and the quality of care. The British are able to implement system-wide actions, such as banning direct-to-consumer marketing of prescription drugs, that seem unlikely to pass in the US, given the influence of powerful stakeholders. The “UK has people in charge of its health care—people with the clear duty and much of the authority to take on the challenge of changing the system as a whole.” For example, the national director for primary care is responsible for primary care policy. The US has no comparable position, although the office of the US Surgeon General often tries to take an agenda-setting role.

British clinicians are generally given a single unified message about how and with what therapies to treat their patients. If NICE and the NHS provide a certain medical protocol, the British patient will receive that care fairly consistently. Unlike the message in the UK, the US physicians rely on FDA approval of drugs and devices as well as clinical guidelines produced by a myriad of professional organizations, and until recently, relatively little unifying national influence counteracted local practice preferences. The American patient typically receives the latest, newest drugs, devices, procedures, and biologics. The American medical community
may be viewed as disjointed, with hundreds of special interest groups and professional organizations, each putting forward their clinical recommendations, guidelines, and agendas. 

Further, the UK and US political organizations allow for different political outcomes of health care reform. The UK is able to perform a “massive” effort to improve the NHS with the Modernisation Plan, begun in 1997. This plan involves huge new investments, raising the spending on health care from 6.5% of the GDP to the current level of about 8% of the GDP, as well as the creation of the National Service Frameworks, whose goal is a strategic plan for new “targets and approaches to care improvement.” These differences will have consequences for the two systems’ implementation of HPV immunization programs.

**Regulatory structures relevant to HPV vaccine approval and distribution**

**The US’s FDA.** The FDA is a division of the US Department of Health and Human Services (DHHS) and is responsible for regulating food, dietary supplements, drugs, cosmetics, medical devices, radiation emitting devices (including non-medical devices), biologics, and blood products in the US. The agency also serves as the licensing authority for new drugs and medical technologies.

As an administrative agency in the executive branch of the US government, the FDA derives all of its authority and jurisdiction from various acts of Congress. The main source of the FDA’s authority is the Federal Food, Drug, and Cosmetic Act. This act gives the FDA various responsibilities including ensuring that “no adulterated or misbranded food, drug, or medical devices enters into interstate commerce.”

The FDA has the power to regulate a whole host of products in a manner that ensures the safety of the American public and the effectiveness of marketed food, medical, and cosmetic products. Regulations may take several forms, including an outright ban, controlled distribution, and controlled marketing. Additionally, the FDA sets the standards under which individuals may be licensed to prescribe drugs or other medical devices. Regulatory enforcement is carried out
by Consumer Safety Officers within the Office of Regulatory Affairs and criminal matters are handled by special agents within the Office of Criminal Investigations.  

The 1997 FDA Modernization Act (FDAMA) amended the Federal Food, Drug, and Cosmetic Act relating to the regulation of food, drugs, devices, and biological products. With the passage of FDAMA, Congress enhanced FDA's mission in ways that "recognized the Agency would be operating in a 21st century characterized by increasing technological, trade and public health complexities." This major new legislation included important provisions regarding patient access to experimental drugs and medical devices, information on clinical trials, pharmacy compounding, food safety and labeling, and addressed pediatric drug trials. One term of the act altered the prohibition on manufacturers' dissemination of information about unapproved uses of drugs and devices, permitting them to disseminate peer-reviewed journal articles provided that they commit to file, within a specified time frame, an application to establish the safety and effectiveness of the unapproved use. The statute also added a new provision that requires tracking of the status of post-marketing approval studies.

FDAMA reauthorized, for five more years, the Prescription Drug User Fee Act of 1992 (PDUFA), which was "the most significant statutory attempt in the 1990's to accelerate the FDA drug approval process." In the past five years, the program has enabled the agency to reduce from 30 months to 15 months the average time for new drug review. This accomplishment was made possible by FDA managerial reforms and the addition of 696 employees to the agency's drugs and biologics program, which was financed by $329 million in user fees from the pharmaceutical industry (PDUFA renewal through 2012 is now before Congress). PDUFA has triggered claims that the FDA has become too dependent on, and embroiled with, industry interests.

Currently, the FDA is divided into five major centers: the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), the Center for Food Safety and Applied Nutrition
(CFSAN), and the Center for Veterinary Medicine (CVM). Vaccines are approved or rejected by CBER, although CDER is the largest of the FDA's centers and is charged with the task of approving or rejecting the far larger number of drugs. CBER is responsible for ensuring the safety and efficacy of blood and blood products, vaccines, allergenics, and biological therapeutics. CBER's regulation of biological products has expanded in recent years to include a wide variety of new products such as biotechnology products, cell therapy and gene therapy, human cells and tissue-based products.

**The US's ACIP.** ACIP, within the Centers for Disease Control and Prevention, is not a regulatory body but its goals are to provide advice that will assist the US DHHS and the country in reducing the incidence of vaccine preventable diseases and to increase the safe usage of vaccines and related biological products. ACIP consists of 15 experts in fields associated with immunization who have been selected by the Secretary of the US DHHS to provide advice and guidance to the Secretary, the Assistant Secretary for Health, and the CDC on the most effective means to address vaccine-preventable diseases. ACIP's statements are official federal recommendations for the use of vaccines and immune globulins in the US and become CDC policy when they are accepted by the director of CDC.

The Committee develops written recommendations for the routine administration of vaccines to the pediatric and adult populations, along with schedules regarding the appropriate periodicity, dosage, and contraindications applicable to the vaccines. To ensure thorough review of available information, ACIP often appoints working groups to assist drafting its recommendations, comprised of ACIP members, CDC staff, and others with immunization expertise. ACIP is the only entity in the federal government which makes such recommendations.
**The UK's NICE.** NICE is a SHA established in 1999 in order to assess the clinical effectiveness of treatment regimes and health technologies in Britain, as well as to provide guidance in promoting public health standards. NICE publishes clinical appraisals of particular treatments that may be determined to be worthwhile by the NHS, based primarily on the criteria of cost/quality-effectiveness.  

Unlike the US FDA, the UK's NICE does not license medical technologies. New drugs must first be licensed by two regulatory bodies before they can legally be used in the UK or considered by NICE for the NHS formulary. The European licensing agency is the European Medicines Evaluation Agency (EMEA). The specifically British licensing body is the Medicines and Healthcare products Regulatory Agency (MHRA). Vaccines primarily go to the EMEA.

Candidates for technology assessment must be referred to NICE by the Secretary of State for Health. An independent academic center analyzes all of the published information on the technology under appraisal and prepares an assessment report. The process aims to be fully independent of government and lobbying power. Unlike regulation and licensing of new therapies, which usually focuses on their quality, safety and efficacy, in the case of drugs, NICE is mandated with judging primarily cost-effectiveness. The institute is explicitly directed to weigh both the health gains and costs of that technology relative to current best medical practice. This process takes into account both desired medical outcomes, the best possible result for the patient, and the economic arguments regarding differing treatments. From this review, NICE develops recommendations and clinical guidelines which are then issued to the NHS.

Since its launch, and its first "negative" decision on the anti-influenza drug Relenza, NICE has been at the center of international attention, and it has been seen as a potential mechanism for "rationing access to new expensive therapies." An increasing number of European countries are now adopting the UK NICE approach by putting in place systems that
require evidence of cost-effectiveness of drugs, devices, and biologics, including vaccines, often at the time of market launch.\textsuperscript{84}

NICE carries out assessments of the most appropriate treatment regimes for different diseases. On its own, clinical effectiveness is insufficient to receive NICE approval. Cost must also be taken into account. When good evidence of the therapeutic equivalence of two or more clinical management strategies, the cheaper option is preferred in Britain.\textsuperscript{84}

NICE has set up several National Collaborating Centres that draw up the boundaries of the guidelines. The National Collaborating Centre then appoints a Guideline Development Group whose job is to work on the development of the clinical guideline. This group consists of medical professionals, representatives of patient and professional groups, and technical experts. They work together to assess the evidence for the guideline topic including the clinical trials of competing products before preparing a draft of a guideline.

During two consultation periods, stakeholder organizations are able to comment on the drafted guideline. After the second consultation period an independent Guideline Review Panel analyzes the proposal, and the stakeholder comments to ensure that these concerns have been taken into account. The Guideline Development Group then finalizes the recommendations and the National Collaboration Centre produces the final guideline. This guideline is submitted to NICE that then formally approves it and issues this guidance to the NHS.\textsuperscript{4}

Though NICE does not evaluate vaccine cost-effectiveness or approval, its work directly intersects the HPV vaccine policy when the whole expenditure on cervical cancer prevention is addressed. The HPV vaccine adds a very large price tag to the NHS’s Pap smear screening and LBC, which are already in place and in the budget. NICE does not have a straightforward or simple job. Rationing health care in the UK and the US is inevitable with a finite amount of resources. However, the UK’s tightly organized national system makes the rationing more transparent than the public-private hybrid system of the US. NICE, however, continues to inform NHS decision making, encouraging the use of effective and safe therapies. NICE's
appraisal focuses not only on service enhancement, but also on withdrawal of existing ineffective or inefficient therapies, attempts to promote a more effective system and better patient outcomes.\textsuperscript{84}

**The UK's JCVI.** The Joint Committee on Vaccination and Immunisation (JCVI) is an independent expert advisory committee to the UK Department of Health established in 1963 that performs the same function as NICE, except that it deals exclusively with vaccine implementation. Their goals are "to advise the Secretaries of State for Health, Scotland, Wales and Northern Ireland on matters relating to communicable diseases, preventable and potentially preventable through immunisation."\textsuperscript{85} The advisory body makes recommendations to the British government concerning mandatory vaccination schedules and vaccine safety.\textsuperscript{85} The Committee is made up of representatives from numerous public health and clinical backgrounds including physicians, nurses, epidemiologists, and lay people.

The JCVI's regulatory process is very similar to NICE's process, including its ultimate emphasis on cost-effectiveness. After a new vaccine is licensed for use in the UK, a subcommittee with the necessary scientific expertise is formed to review the evidence and to commission additional research on the vaccine. For example, the subcommittee may want to poll public opinion about a new immunization popularity or age-appropriateness of vaccine dosing. Once the subcommittee has reviewed all vaccine information, they write a report that is then reviewed by the main JCVI. The main JCVI focuses on larger, less-scientific policy issues such as how the vaccine will work with the rest of the recommended immunization schedule, how it will work with the health service logistically, what are implementation barriers, and what are the social implications.

The JCVI also performs research looking at the whole of the immunization program in the UK. They keep a constant overview on vaccine coverage in the country. They look at whether vaccine schedules need to be modified, whether new at-risk groups need to be added,
and whether there should be an extension of use of a certain vaccine. NICE is also at least an indirect part of the HPV policy story in the UK, because NICE is responsible for regulation of Pap smear technology, and a wrinkle in HPV policymaking, as noted earlier, is that Pap smear screening needs to continue even after vaccination.

Comparing US and UK approval processes

In both the US and the UK patient access to pharmaceuticals is a result of the interaction of several variables: marketing approval, time of marketing approval, coverage, cost sharing, conditions of reimbursement, speed from marketing approval to reimbursement, and the complete supply/stock of drugs to the population. The debate on access to new drugs has focused on the time lag between applications for approval and granting of marketing authorization. This delay was identified as a “major barrier with respect to patient access to new drugs, encompassing the hurdles of safety, efficacy, and quality.”

One research group comparing the two systems reviewed 38 NICE guidance appraisals that included 71 recently approved drugs considered to have either high clinical or cost benefit. Of the 71 drugs, the FDA had approved 64. The subset of 64 drugs received marketing authorization in the US prior to approval in the UK. On average, US health plans covered 87% of the 64 drugs, the same percentage of drugs recommended for NHS reimbursement and use. Cost sharing in the US was significantly higher than in the UK, with wider variation across plans. Only 15% of drugs covered in the US had conditions of reimbursement, while 46% of drugs in the UK had conditions of reimbursement. US plans were quicker to decide to reimburse drugs following marketing approval than was NICE. The group concluded that the US provides faster, more flexible access to most, but not all, of the UK-approved pharmaceuticals in their sample. However, US patients have higher cost-sharing responsibility than the UK patients and coverage is less evenly spread across the population.
From a policy perspective, the study findings confirmed that therapeutics are approved faster in the US than in the UK, leading the study's authors to suggest that the "need to bolster the NICE fast-track initiative to decrease the amount of time it takes to appraise certain new pharmaceuticals." The study findings also point to the need in the US for careful monitoring of post-marketing data to assure that the faster approval process does not leave patients unprotected. Gardasil may illustrate the relative paces of these processes: the FDA approved Gardasil's use in the US before it was approved in the UK by the JCVI.

The FDA approval process results from trial data that are small enough in size – even though they may contain thousands of patients – that uncommon, serous adverse events can go undetected before approval, and adverse events are also thought to be significantly underreported in postmarketing surveillance. This underreporting is largely without consequences to the manufacturers, since the FDA lacks authority to pursue companies who violate regulations and ignore post-marketing safety study commitments.

NICE works with the Commission for Health Improvement (CHI) to improve drug and patient safety. NICE is able to evaluate and recommend therapies, but CHI, also founded in 1999, reviews safety and implementation data of the guidelines. To help improve the quality of patient care they assist the NHS in addressing unacceptable variations and in ensuring a consistently high standard of patient care.

Both the FDA and NICE attempt to balance the speed of drug approval with patient safety. If they are to provide advice at the time of market authorization or shortly thereafter, it is hard to say with confidence "that there is an acceptable evaluation of safety without the post-marketing surveillance." Obviously, the same concerns apply to the approval and postmarketing surveillance of vaccines.

DTCA of prescription drugs – and, as the Gardasil example makes clear, of vaccines – is now legal in the US, but it is illegal in the UK. For decades manufacturers promoted drugs and medical devices exclusively to physicians. Given the paternalism that was typical of
physician/patient relationships in the mid-twentieth century, promoting prescription drugs to the public was unthinkable. Only in 1981 did the pharmaceutical industry first propose changing its marketing approach to include consumers. Not until 1997, following a public hearing and debate, did the FDA issue a draft proposal for new guidelines on broadcast DTCA. For the first time, manufacturers could give both the drug’s name and the condition without disclosing all of the product’s risks. However, advertisers were required to mention important risks and to provide a statement explaining that additional information is available from other sources.64

Debate about the advantages and disadvantages of DTCA is increasing. Proponents argue that it serves an educational mission. Opponents argue that it “is contradictory to have a category of drugs called ‘prescriptions,’ made available through those with specialized training, yet allow those same drugs to be marketed to persons who lack that specialized knowledge.”64 Physicians feel that TV advertisements lead patients to overestimate a drug’s benefits and underestimate its risks 65% of the time.60 These questions arising from drug studies need to be kept in mind as we consider the possible influence of DTCA on HPV vaccine distribution.

As health care expenditures have risen over recent decades, demands for proof of cost-effectiveness of medical technologies and services have increasingly emerged as a tool for decision makers seeking to ensure the delivery of health care value for money spent. The UK has embraced this strategy more explicitly than has the US. Perhaps the US and the UK can each advance by studying each other’s successes and failures to find the right health care prescription that is safe, beneficial, and cost-effective.

Critical Policy Influences on Distribution of the HPV Vaccine

Guidelines are more likely to reflect than to cause policy paradigms for any given therapeutic question. Because, as a rule, guideline development requires the cooperation of multiple stakeholders, even in health "microsystems," guidelines may well be compromise documents, products of alternative interpretations of best available medical evidence (limited as
the evidence almost always is). For this reason, a brief review of extant HPV guidelines can suggest the policy limits bounding the implementation of HPV vaccination programs.

**HPV guidelines in the US**

A search of www.guidelines.gov produced six guidelines directly dealing with the HPV vaccine as a preventive measure. The guidelines were sponsored by ACIP, the American Academy of Family Physicians, the American Academy of Pediatrics, the Institute for Clinical Systems Improvement (a private nonprofit organization based in Minneapolis), by ACOG, and the American Cancer Society. The most recent STI guidelines from the CDC advise condom use as a means to prevent HPV infection. Specifically addressing the vaccine, the CDC's Advisory Committee states that the vaccine is considered highly effective in preventing infections that are the cause of most cervical cancers. ACIP voted to recommend that the vaccine be given routinely to girls 11-12 years old. The ACIP recommendation also allows for vaccination of girls beginning at age nine as well as vaccination of girls and women 13-26 years old. On August 8, 2006, ACOG released its HPV vaccine recommendations. ACOG recommends that HPV vaccination be offered to all girls and women 9 to 26 years old who have not previously been vaccinated. All agree that the vaccine should ideally be administered before onset of sexual activity (i.e. before women are exposed to the virus), but females within this age range who are sexually active should also be vaccinated. ACS recommendations are similar.

The ACIP recommendation supports making quadrivalent vaccination the standard of clinical care. However, it is important to emphasize that the vaccine is supported by limited efficacy and safety data. Clinical trials have thus far involved a relatively small population (<12,000 participants) for a limited period of follow-up (5 years). The vaccine has not been evaluated for efficacy among younger girls (aged 9 to 15 years). Yet, if the vaccine were required nationwide, it would be administered to some 2 million girls and young women, most of
them between 11 and 12 years old and some as young as 9 years old. The longer-term effectiveness and safety of the vaccine still need to be evaluated among a large population, and particularly among younger girls.43

The HPV prevalence study, NHANES, found that 3.4% of women aged 14 to 59 were infected with one of the four HPV strains covered by the Gardasil vaccine—strains 6, 11, 16 and 18. While 3.4% may not seem like a large number, the CDC's Dr. Lauri Markowitz stresses that, again, this figure is reflective of a "point in time" and does not demonstrate a woman's lifetime risk of picking up these particularly dangerous strains. "So, this doesn't change our thinking about our [vaccine] recommendations," she says. "It substantiates the evidence that is already out there." The CDC divides potential vaccine recipients into the naïve to all 4 vaccine HPV types, who can derive maximum benefit, subjects with ongoing/prior infection with <4 vaccine HPV types, or "partially exposed" women, who can derive some benefit, and subjects with ongoing/prior infection with 4 vaccine HPV types, or the "fully exposed," who will derive little benefit.39 ASIP says that in the general population of 16-to 24-year-old North American women, most are naïve to all four vaccine HPV types with few positive to both HPV 16 and 18, even with four lifetime sexual partners (LSP) and even with a prior Pap test abnormality. Therefore, administration of Gardasil should be highly effective at reducing the burden of HPV disease and the benefits of Gardasil will become more apparent over time.39

HPV guidelines in the UK

On June 20, 2007, the Department of Health agreed, in principle, to accept JCVI’s advice that HPV vaccines should be introduced routinely for girls aged around 12-13 years, subject to independent peer review of the cost benefit analysis, and should be paid for by the NHS. Routine vaccination of girls could start as early as autumn 2008. Details of the program will be finalized over the next few months, following further advice from JCVI and discussions with the NHS on the implementation of the program.
The JCVI has advised that HPV vaccines are clearly beneficial. The commissioned cost-effectiveness analysis is currently the subject of an external peer review. The JCVI is expected to make its formal recommendation to the government at their next meeting on October 17, 2007. According to the Department of Health the cost will be £300 per full course. However, importantly, no ‘catch up’ program for the 14 year-olds and upwards was mentioned within the JCVI recommendation. RCOG and the Royal College of Midwifery have been waiting on the JCVI decision before making a professional recommendation about HPV vaccination and reporting their public opinion statements.

Some vaccine issues with which the JCVI is grappling carry more weight in the UK than they have carried with US opinion leaders. The JCVI is concerned about the economics of a vaccination “catch-up” for females already older than 11-13 year olds who may be “scheduled” to be vaccinated, but are younger than 26. The prevention of genital warts is also playing a larger role in the discussion than anticipated. The US officials cite the benefit of reducing the incidence of genital warts, but UK policymakers turned a particularly strong light on this health outcome. Neither “catch-up” populations nor the burden of disease of genital warts played a significant role in the US policy debate.

Dr. Andrew Hall who is the JCVI chair as well as the JCVI’s HPV sub-committee chair explains that “‘catch-up’ in the US is used slightly differently from ‘catch-up’ in the UK. In the US, the way the ACIP uses it, they recommend that any woman up to 26 can be vaccinated with the HPV vaccine. That just means that they go out and buy it for themselves or they are eligible for it under the appropriate program. And that would continue forever if they were in the age range. In the UK, what we mean by a ‘catch-up’ is slightly different. We mean that, at the time of introduction of a vaccine, you do a mass vaccination of the older age groups who basically will have missed out because they are not scheduled for it. And it is a once-off event because once you’ve done it, everybody older is vaccinated so then the schedule just sweeps forward and the cohort should be vaccinated.”
The importance of genital wart reduction in the UK policy discussion may have an effect on choice of vaccine — assuming that the GlaxoSmithKline candidate also wins approval — and on estimations in the cost effectiveness analyses. Dr. David Hicks, an RCOG member and NHS hospital director, says "The benefits, of course, are not simply from the reduction of cancer risks. It is as effective, it is believed, against 6 and 11, notably. And, it is going to cut down on genital warts. I don't know what the costs would be, but that is something that needs a lot of public health intervention... As a GU (gynourological) physician, 40-50% of my work was related to genital warts. It is a present-day epidemic for which only medieval treatments are applied... The only 20th, 21st century approach is Aldara... This could be an answer to that. [Aldara's expense and limited efficacy]... So, I think that it has spin-off advantages as well as the reduction in cervical cancer, squamous cervical carcinoma... For example, we believe that HIV is facilitated by other infections. And it may be that having more skin that is available to become traumatized during sex, or skin that is pretty vascular usually can break. Now it may be that having warts, that have those properties, can facilitate HIV. So it may be that another spin-off is that you reduce HIV in the longer term."

Hall reiterates the fact that genital warts are a significant public health issue and one that plays into the JCVI decision-making process. "There are about 100,000 cases a year in the UK, so it's not trivial. There is clearly a benefit of preventing genital warts. So in general, you would prefer a vaccine that did both, but ultimately, because of the amount of infection, it will be the cost-effectiveness which will determine which vaccine is used."

According to Hall, "the main questions to be addressed by policy [in the two countries] are very similar. Should we vaccinate boys as well as girls? What is the optimal age? This catch-up business... I think those are the main issues... And method of delivery because you don't automatically have the vaccination at the possible age you are looking at. Could you reconstruct the school vaccination program easily and cost-effectively?... Should it be done through primary care settings?... a number of issues around that that are yet to be resolved."
The UK has an immunization delivery system through primary care clinics and school nurses. School booster doses are administered through a school program. This fact plays into the decision of what age should be recommended for vaccination. Hall says, “Then the issue of whether it should be primary school, which here is around the age of 11 or 12 or secondary school, which is from 12 on. So do you go for the last year of primary school or the first of secondary school? And there are a lot of issues around the fact that primary schools are generally smaller than secondary schools so you get into scales of efficiency. This is another thing that informs the decision on catch-up because, at the moment, students can leave at 16 if they choose, although the majority stays on until 18. So you can potentially do a catch-up till 16 pretty easily. You could do a catch-up to 18 in the majority relatively easily. But how do you do a catch-up beyond that? There is no obvious way that young fit women will access health care that would allow you to offer the vaccine. So those are the kind of issues the main JCVI has to grapple with when it makes a recommendation.”

Frequently, more than one vaccine is available to protect against a single agent. However, in the case of Gardasil and Cervarix, the two significantly different HPV vaccines create additional issues that need to be considered. According to Hall the new logistical questions with these vaccines include, “Would you buy one vaccine or two? Would you buy some proportion of each? How much would you buy? Can use them together—can you give a second dose of a different vaccine in the same course? Because otherwise you would have to have some geographical separation of the two vaccines within the National Health Service. So yes, depending on the cost-effectiveness comparison between the two vaccines your first choice would be the most cost-effective including genital warts in the cost-effective analysis. But then...if the two vaccines showed identical cost-effectiveness you would choose the one that prevented genital warts, wouldn’t you?”

Currently, the HPV vaccine is only available through individual PCTs who have voted to offer the vaccine and private clinics outside of the NHS. As Hicks points out, "If this thing has a
license, then it is available to the NHS. The cost is, of course, the big issue. And at the moment, left to the Primary Care Trusts to decide whether this is something they offer. But for expensive treatments not every PCT will adopt it. So, you will have areas in the country where it is available and areas where it isn’t. And that it is not systematized means it is not going to work the way we wish it to in the future.”

The non-profit reproductive health clinic Marie Stopes International (MSI) offers the vaccine for a fee. Tony Kerridge, the Senior Communications Manager-Press and Public Affairs at MSI reports, “With any number of things the private sector starts offering things long before the NHS can, or is able to, embrace it. We even can offer it before NICE looks at it. As soon as it is licensed, we can offer it. However, we are, obviously, not for profit, so the people who come to us pay a fee. We were pretty much the first, if not the first, to offer the Gardasil vaccine [in the UK]. But, we can only see those that can afford to pay.” The clinical services manager at MSI, Sue Baldock, SRN, comments, “We started offering Gardasil in November, the minute we could get hold of it. But because there wasn’t much media on it—we did a sort of launch on it—but you don’t read about it in the papers.”

Baldock speculated before the JCVI approval that “it seems that only private providers are offering it. The National Health Service won’t take it on because of cost. It’s £450 a treatment. So automatically, you have a social divide. We have public school girls coming with their mothers because they are phoning us up and sending them in” ["public" schools in the UK are actually private, and usually attended by students from more affluent families]. Kerridge continues, “It’s a double thing. The well-to-do mothers are much more likely to read the right newspapers and be informed about these issues. As always, the less well-to-do, the less able and the lower social class are always the last to receive the things like this, which is a great shame. They are the ones that actually need it.”
Different Incentives and Perspectives

The US and UK approach health policy from different perspectives and with different motives. In general, prevention does not have the high profile in the US that many in the health services community would like it to have, whereas prevention more clearly and significantly benefits the British system. The American medical system's finances and reimbursement patterns are structured on use of health services, especially procedures, and not on preventing disease. American insurance companies do not insure lives from birth to death; American insurers do not readily see a case for paying for prevention the benefits of which might only be realized down the road, and by another insurer. By comparison, the NHS saves money when people do not get sick and do not use additional health services use their health care system. The UK captures the health savings of prevention; the private part of the American health care system only makes money from disease; and although the public part of the system could, as does the NHS, realize the economic benefits of prevention, its financial structures remained tied to use, rather than to the absence of use; it is also true that the public parts of the system, such as Medicare, may inherit the consequences of too little preventive health care at earlier points in Medicare recipients' lives. These dynamics lead to an American system in which we welcome new technologies and therapies, encourage their use, and bear – or profit from – the higher costs of the new technologies.

British health care has not only different incentives, but also is seen as a "public good" according to Shelia Leatherman a health care policy analyst and consultant. "Health is viewed as a public good in Britain, Europe, and much of the world. Here in the US it is regarded as a private good, as any other commodity or any other commercial good, like TVs and washing machines. The UK has a more integrated approach to life with government involvement when it comes to health care...the government regards itself as having a stewardship role in acting in the public good. Whereas, in the United States, by contrast, I think we have very low tolerance and pretty low interest in terms of federal health policy, unless it has to do with money."
US State mandates

The complexity and multiple points of access and control in the US system raise additional challenges for a coherent HPV vaccination program with which the UK does not have to struggle. Merck, being the first licensed HPV vaccine manufacturer, heavily promoted its product to attempt to take full advantage of its solo spot in the marketplace. Merck aggressively lobbied state legislatures to pass mandates that required vaccination for school attendance, primarily for sixth grade girls. Dr. Alan Cross, a US pediatrician and adolescent medicine specialist at the University of North Carolina at Chapel Hill notes, "[GSK's vaccine] will be approved very soon, and so it is clear that Merck is working hard to get as much of their vaccine consumed while they have the sole one on the market, as soon as possible. I do not begrudge them that." Among other marketing activities, Merck provided significant financial support for Women in Government, a "national non-profit, bi-partisan organization of women state legislators providing leadership opportunities, networking, expert forums, and educational resources to address and resolve complex public policy issues." Allina, the Program and Policy Director at the National Women's Health Network (NHWN) in Washington, D.C., noted that Merck's very deliberate agenda-setting effort raises "red flags." Some of the biggest and reddest of the flags surround the question of state policies to mandate vaccination, a position taken by Women in Government.

The media attention resulting from the state mandate issues has both helped and hindered the successes of Gardasil. Social awareness for cervical cancer as a health issue and the effects of HPV infection has dramatically increased as a result of the political controversy. However all the attention has also raised concerns about the vaccine efficacy and safety with both medical and public observers alike. Lisa Goldstein, Director of Adolescent Health Care and Health Care for Underserved Women at ACOG, says that, "We receive a lot of calls from people with questions about the safety of the HPV vaccine. Was it well tested? What are the side-effects? and things like that. So I think all the discussion about the mandates has raised
awareness even more about the HPV vaccine, which is a good thing, but it also raises skepticism. People are just questioning what is the safety of the vaccine? Should it really be implemented already? That is sort of what we've been seeing." Goldstein continues, "Because Merck pushed it so heavily, it has led to some skepticism about the policy, not just with providers, but also with patients. With so much media about the vaccine I think that people start to wonder... 'is it something they just want to make money off of, or is it really effective?'"

The CDC has published research establishing school mandated immunizations as an excellent tool to encourage high levels of vaccination, as has been the case with mandates – via, for example, school entry requirements – for other vaccines. However, ACOG's Goldstein reports, "We have a statement in general about school mandates, but we don't specifically say the HPV vaccine should be a mandatory vaccine for school entry. There are some concerns raised about mandates. If you are going to mandate it, the cost—it's a very expensive vaccine and the supply has to be there. The physicians have to be providing the vaccine. Again, if you are going to mandate it, then you have to have somewhere patients can go to get it. So it's really pretty early on, from our perspective, to be pushing school mandates. There is not really the infrastructure to do it yet. That is how we've been guiding our section leadership in terms of these things. But we don't have a formal position saying one way or the other, yes or no."

ACIP's HPV scientific director Dr. Lauri Markowitz notes that the CDC was "a bit surprised about the level of lobbying that went on because no one really felt that there would be a push for mandates this early. But...it has really created a lot of the controversy that we are now seeing..." She notes that "there are groups that are anti all vaccines in general and then there are people that are opposed to mandates specifically. These people have all coalesced around the mandate issue."

Media coverage of the mandate debate has focused new attention on a major women's health issue, which is not used to the limelight. NWHN's Aliina says "It is typical for a new drug [to] get launched with a huge amount of media hoopla...It does not often happen on that scale
in the reproductive health world. So in that sense this is a little unusual, but because it is being presented as cancer prevention, it is maybe being treated by the industry a little bit differently than other reproductive health products."

According to Dr. Lawrence Goslin of Georgetown University, an observer of the state mandate discussion, "concerns about mandatory HPV vaccination are not motivated by morals as there are no data to suggest that an appropriately conducted public health program encourages sexual activity [many would disagree with Dr. Goslin that "morals" are not motivating at least part of the mandate debate]. Rather, maintaining the public's trust is vital—both for HPV vaccination in particular and for school-based vaccination programs more generally...there is nothing more important to the success of public health policies than to ensure community acceptability." In this view, legislation to make HPV vaccine mandatory has undermined public confidence and created a backlash among parents and the public in general. ACOG's Goldstein notes, "What we've seen and heard from various groups is that they aren't against the vaccine in general, but they are against mandates. They want people, parents, to have an actual choice in it and not just be told they have to do it. So, many of the state mandates are including an opt-out...I don't even think it will affect state mandates. But it's a little soon to say."

UNC's Cross: "I think the Texas example is a good one. You have a conservative state, a Republican governor who jumps right on board to promote the vaccine, and then it turns out he is in the hip pocket of the drug industry and his motivation is not the betterment of girls with the diminution of cervical cancer. So that certainly confuses the whole issue and if you have our government scientific leaders making statements in favor of the vaccine and then discover that they are being paid under the table, or over the table, it causes you to lose confidence in their judgment...you have the fox and the wolf guarding the chicken house. There are not consumer advocates that are sort of built into that system, who are there to be skeptical about the value, and that is incomplete regulation. I think that raises questions about the validity of the claims"
that people are making and forces me, as a health professional to the public, to really look behind the expert advice to try to find out about what the real truth is, when, in fact, we should have committees that are there to do that for us and honestly represent the real truth...So, that is my main reservation. I do not know of any scientific invalidity [and] have not yet faced the question of whether one of the vaccines is better than the other...I cannot count on others to tell me the answer. There will be inadequate data to make the decision because it is all too early.”

**MMR vaccine-Autism shadow and political influences in the UK**

The major parallel to the state mandate discussion in the US is the measles, mumps and rubella (MMR) vaccine-Autism scare in the UK. Its shadow, as political health analyst Leatherman noted, is affecting the direction of current policy. The actual policy decision and policy direction will be as influenced by the political fallout from the MMR incident as it will be for the scientific merit of the HPV vaccine, according to Leatherman.

Controversy over the MMR vaccine began in the UK in 1998 and has continued to the present. In the 1998 *Lancet* paper that started the controversy, Dr. Andrew Wakefield and colleagues at the Royal Free Hospital in London claimed to have identified twelve autistic children with colonoscopy studies positive for a form of inflammatory bowel disease, “autistic enterocolitis.” The authors stated that in eight of the twelve cases the parents credited the onset of symptoms of autism to the MMR immunization they had received, on average, six days before the behavioral changes. Wakefield hypothesized a causal relationship with the MMR causing a persistent measles infection in the gut that was in a distinctive “enterocolitis,” which in turn produces a ‘leaky bowel’ that allows toxic “opioid” peptides (derived from the breakdown of gluten and casein, contained in wheat and dairy products) to enter the blood stream, passing to the brain, these peptides cause autism.”

The authors of the *Lancet* paper agreed that they “did not prove a link between MMR vaccine and this syndrome [autistic enterocolitis].” In fact, they did not provide any evidence
for an association. The suggested “chain of causality is supported only by analogy and speculation.”

Following research looked at the records of 500 children with autism born in London between 1979 and 1998. The group saw “a steady increase of cases but with no sudden ‘step-up’ or change in the trend line after the introduction of MMR in 1988.” Numerous other studies also proved unsuccessful at proving a relationship between MMR and autism.

A contributing voice in the controversy was the parents of the autistic children, some discarded the idea that the autism was a random genetic event and maintained that it was the result, at least partially, of some environmental factor (identified, more or less categorically, as MMR). In the US, parents also fault vaccines for causing autism, but Americans focus on vaccines containing the mercury-based preservative thimerosal. This preservative is a component of the diphtheria, tetanus, pertussis (DTP) vaccine, but not the MMR vaccine.

Of note, the Prime Minister Tony Blair refused to reveal if his youngest son Leo was vaccinated with the MMR. He noted this was a private matter and he continued his support for the official Health Department policy on MMR vaccination. To the British public, Blair’s stand seemed “insincere.” People thought that if Leo had been immunized his parents would have been happy to report the fact. The people’s response was ‘if the prime minister’s family doubted the safety of MMR, why should we trust it?’

The primary dilemma was that the New Labour’s position not in favor of separate vaccines ran counter to one of its central policy themes—“the empowerment of the individual consumer.” This point was made by the National Autistic Society in its March 2002 position statement: “The Government promotes choice in many areas of public policy. In rejecting it here it may fail to recognize assertions of patients’ autonomy and a perception of paternalism may well have caused some of the reluctance to vaccinate.”

The political difficulty that surfaced with MMR vaccination is that “individual choice cannot be reconciled with a mass childhood immunization program.” Population-wide
vaccination is a public health policy to prevent diseases at a population scale, not individual scale. This action calls for individual children to be immunized, while decisions about what vaccine to use to protect against which diseases, can only be taken from the perspective of the public as a whole.

For each child, the question of accepting an immunization balances the benefits and risks. Formerly, this balance was fairly uncomplicated. The risk of an infectious disease was severe; whereas the small risk of vaccine complications was considered worth taking. The current problem with MMR is that as these infections are now rare making the risk of the vaccine larger than before. The New Labour government's promotion of an "individualistic outlook" means that any plea to a communal herd immunity is "doomed." One analyst notes "To criticize parents for making decisions seen as selfish or self-seeking in the climate of consumer sovereignty promoted by New Labour seemed inconsistent."

Given the current culture of concern about health and risk aversion, the MMR immunization controversy has put the national childhood vaccination program in danger. This policy requires parents to allow a small risk of adverse reactions, to avoid a larger public health risk of infectious disease. It also requires that parents follow the recommended timeline for vaccination by bringing in their children to the clinic. In Britain the series includes a total of five visits for 16 vaccinations, up to the age of five; the US schedule involves eight visits and at least 23 vaccinations. Finally, this program requires some trust in the medical community and the policymakers who create the program. In relation to MMR and now the HPV vaccine, the "erosion of trust and the growth of risk aversion have gravely weakened the consensus underpinning the immunization program."

The review of the MMR controversy reveals some of the key features of the cultural environment affecting matters of health and illness in contemporary society. Anxiety around issues of health is reflected in a increased sense of individual vulnerability to environmental dangers and in a general reluctance to risk, particularly in relation to children. This trend
appears skeptical toward science and medicine. The result is the MMR vaccination in the UK has fallen, from a peak of 92% in the mid-1990s to 82% of children age two vaccinated in 2003. In London use is now less than 75%, causing a significant risk of measles outbreaks. Also in the US, the percentage of parents opting out of school-based immunization has increased significantly in some areas.96

From Leatherman's perspective, the MMR controversy looms large in the current political environment surrounding further embrace of vaccines like the HPV vaccine. "The medical profession did not responsibly address this ... physician and the research he did. [His work] got published in Lancet. And then the government handled it very poorly and it really got even more extreme. So there's that in the background," she said, not long before the JCVI recommended adoption of Gardasil. The other thing related to the HPV vaccine is the current political policy dynamic in both countries...it is risky for them to do so [go forward with a recommendation in favor of Gardasil, because of the MMR controversy]. As a result [of the controversy], the MMR vaccination rate dropped off dramatically. And the government was not regarded as a trusted protector of health. The department of health really ran into a lot of problems. So, taking any position now on a new vaccine must be making them a little bit nervous."

The British public may have blamed the wrong people for its suspicions about the MMR vaccine. Leatherman continues, "The public turned on the government and that's why this is so politically sensitive. It was a shock to the government because almost always in all the public polling literature the public view of the NHS is that it is a cultural and social icon. They are extremely proud of the NHS as basically a symbol of equity and fairness...and believe that the government is acting in their best interest. So for the public to get high jacked by an individual physician, turn on the government and regard them as suspect was a shock. And I think it is a shock that is going to influence, if not their decision, the timing, the release, the communication of any new vaccine."
Ultimately these fears and false assumptions about causation have led to the JCVI and the British Department of Health treating the HPV vaccine as a "sensitive issue." The JCVI chair, Hall began his interview with, "Just to say up front there are some things which I am happy to describe, the process, but I can't say much about decisions that have not been made public."

Another behind-the-scene UK political dynamic, according to Leatherman, is that the HPV vaccine's introduction in the next year will entangle it with Gordon Brown's inheritance of Tony Blair's leadership of the Labour Party, and the necessity of Brown's calling a general election. Gordon Brown as the Chancellor of the Exchequer under Tony Blair was directly responsible for making a "truly historic" decision to increase the percentage of GDP funding for health, which had been historically low in the UK—about 6.5 to 7%. Over a period of five years, a huge infusion of funds including a new tax on the public has been created to raise the UK GDP percentage spent on health care to that of other European countries. "The Tory leader is David Cameron, a rather young, very energetic, kind of new face for the Tories and he is making health one of his main platforms. But the point being that, somewhere, either small or large, will be this issue of whether the government wants to take the risk on something that had so much public outcry and foment five-ten years ago, particularly when the Labour party is considered very vulnerable for a Tory win in the next election. Additionally, some of the [Labour] reforms done with all the best of intentions introduce privatization and consumerism and informed choice... [and] are unleashing a lot of the dynamics that can be counterproductive. So that would be the politics behind the scene."

**Paradoxical Policy Differences in the US and UK**

Despite the vastly greater number of points of access, the strength of competing interests, and the weaker authority of the US FDA, its approval processes can actually seem
more straightforward than those in the UK, at least in the early stages. In the US, once the FDA has approved a vaccine, marketing begins, and the new product enters the list of available therapies (with the caveat that different insurers may make different reimbursement decisions). In contrast, the British approval process is less linear. Until the British system reaches a decision about NHS coverage, there is no systematic way to implement a licensed vaccine. Once such a decision has been made, of course, UK policy becomes more singular and tractable than is US policy.

In the US, once the FDA approved the HPV vaccine for use in females aged 9-26, the American medical opinion leaders made their clinical recommendations for immunization. All major medical groups with authority to speak on cervical cancer treatment and prevention — the ACIP, CDC, ACOG, American Academy of Pediatrics (AAP), and ACS — recommended that the HPV vaccine should be standard of care for girls, targeted by age rather than by level of sexual activity or potential risk. Additionally these groups realized the benefit of congruity in their statements. Not only does each of their recommendations validate the others; the groups' decision to speak as a chorus, with a single message, reduces confusion.

The CDC's ACIP HPV sub-group chair Dr. Janet Gilsdorf illustrates this: “the recommendations that we made are in concert with most other recommending bodies. The American Cancer Society did change their recommendation for over age 18, so 19-26 years old is not quite as strong as ours is. We had a member of the ACS on our working group as well. The ideal is when recommendations can be consistent... So there is a big effort to try to lend some consistency between groups in terms of recommendations, even though we are making recommendations for different constituencies.... We make recommendations to the CDC and the CDC recommendations are designed for the public health sector to give guidance to the state health departments and local health departments who are providing vaccines to their populations. The American Academy of Pediatrics, for example, makes recommendations for
pediatricians in practice. They are not exactly the same constituencies and they do have different ways to look at things, different issues, but those all get discussed during these meetings."

A logistical barrier in the US for widespread HPV vaccination is the practice location in which the vaccine might most frequently be discussed. Obstetrician/gynecologists (ob/gyns) are likely to be asked about the vaccine, especially by their late adolescent and early adult patients, but ob/gyns do not routinely offer and provide vaccines, in contrast, for example, to pediatricians’ familiarity with immunizations. Since ob/gyns are not routine vaccinators, they will require training and a resulting period of traversing the learning curve, according to Goldstein.

Surprisingly, British vaccine regulatory policy is more complex; even British members of the NHS to whom I spoke did not necessarily understand the whole process. The British licensing procedure is carried out by two bodies, a national one, the Medicines and Healthcare products Regulatory Agency (MHRA) and the European licensing agency, the, The European Medicines Agency (EMEA). The former is subsumed in the latter. Vaccines largely go to the EMEA. According to Hall, “In order to get licensure, they have to go through pretty much the same procedure as the FDA. They submit a portfolio, which is then examined. They are then asked questions by a monitor and respond accordingly. Then a committee looks at it and it is, or it isn’t, approved. If approved, the vaccine is then licensed for use in this country, which means that anybody can legally receive it, but it will not necessarily be funded by the government.”

Drugs, devices (including Pap smear screening technology) and other therapeutics are then subjected to a new review for effectiveness and cost effectiveness by NICE. Vaccines are reviewed by the JCVI. Hall describes the process: “they examine all the evidence for effectiveness and otherwise, which for new products is usually pretty straight forward because if they have been licensed, they must be effective. Additionally, they look at cost-effectiveness.
There is a threshold, approximately £20,000-30,000 per QALY, quality adjusted life years... The Treasury will not approve the use of a drug which greatly exceeds the cost threshold."

Once NICE comes forward with a recommendation and says a drug is effective, then in general the doctors of the NHS can prescribe the drug and the government pays for it; EMEA and MHRA licensure but an absence of NICE approval means that patients can, theoretically, get the therapeutic, but must pay for it themselves. Hall comments that "In general the things that do not get NICE approval are expensive and therefore would be expensive for the patient to afford. The big [flap] around this is around cancer drugs because a lot of those are extremely expensive... So then people say the government is letting me die because they won't buy me the drugs—makes good headlines... So any new vaccine is a major issue. Anything that would require substantial money is a major issue, or anything that is tricky ethically. The main committee does not contain all the expertise on every topic. So they create a subgroup that does contain all the expertise that is required, who look at the evidence, draw it all together, write a report, come up with a proposal which comes back to the main committee... [the main committee] either adopt or modify the proposal into a recommendation."

About the HPV sub-committee, which met three times, chair Hall said "Two pieces of work were very important to us. First was to know what the age-specific prevalence of infection of individual papilloma viruses was from the age of 10 up to 25 because one of the big issues was at first at what age should you start recommending the vaccination schedule. So you have 8, 9, 10, 11, 12. Second, and more importantly, was the catch-up... So it is a very complex model. That work is completed, but because of its significance for a major financial investment and also the importance of getting it right for the population, it's gone out to referees. It goes out to external referees whose expertise is in modeling and economics. Now we are waiting for that critique to come back to see if the model needs to be modified and what has been done and then a decision can be taken... And then we can make improvements so that the estimate then that comes out will go to the main JCVI based on all the work that has been done with
regard to the evidence. And the main JCVI will then discuss it...because there is all the heavy-weight science in the subgroup, the main JCVI then looks at what the subgroup is less qualified to do: how the vaccine will work with the rest of the schedule, how it will work with health service, what are the social implications. They look at all the less scientific, but very important policy questions. And we discuss what the popular response might be and how to deal with it—implementation strategies and poll data—stuff like that... I sometime think that we should have something on the website that makes the process transparent. I think most people still don’t understand it who aren’t involved in it, which is unfortunate.”

The waiting period from vaccine licensure to JCVI approval leaves a window of time during which no national recommendations guide British clinicians. As a result, NHS’s Hicks says, “the background at the moment is confusion... Mothers, usually, are approaching primary care GPs to get their daughters vaccinated. There are private means to get this vaccine. I have come across Gay men’s websites and sexually transmitted infection screening clinics in London who offer Gardasil to men. And what you need is some policy. There isn’t even a set of guidelines from the College, say the College of General Practitioners to help doctors. So at the moment, it is very disorganized... [but] it can best be applied in a health economy such as we have in this country. If it were left to the less centralized system like the US...there are standards and guidelines, but they are very much more disparate. Individual organizations have different takes. There is at least a framework with the NHS: a few colleges that set the standards. There is, at least a central bureaucracy that can set mandatory targets. So if it were going to work, it would work somewhere best like the health economy of the NHS. I do believe that.”

Hicks optimistically comments that “it is a matter of ‘grasping the nettle’... What it means is that you are going to bear a little bit of pain, but you’ve gotten rid of a problem. So I think it is going to be worth it, and it needs the health economists to tell us that yes, we are going to spend £90 a shot for three shots. But yes, not only are we going to save on the thousand of
women who die a year from cervical cancer in this country, but we are going to save on the thousands of people who come and use buses and take time off and disrupt their lives to go to GU clinics because they have warts."

During this time period Merck's pressure on the NHS and policy advisors has been more intense than with other drugs and vaccines. JCVI's Hall comments that “the vaccine manufactures, one of the two, has bombarded doctors and people who commission public health services quite hard...And we've also had some [aimed] essentially toward the political process, which is not really that surprising as they see themselves making a great deal of money out of it.”

However, the US and UK do handle pharmaceutical input in their regulatory processes differently. Hall says “In the UK we do not allow any manufactures to attend our meetings. Our meetings are closed and not open to the public. They are not open to any observers unless they are invited. Whereas in the US, the reverse is true. There meetings and dealings are made in the corridors, not in the meetings...manufacturers...influence the decision-making."

The US and UK do share some policy making information. The CDC's Markowitz says, “We exchange information. We don’t actively keep track of that, but we are aware of different things going on.” The UK does keep closer tabs on the US. Hall says, “The JCVI does take a lot of interest in what happens in terms of vaccine policy in the US. So the secretary of the JCVI attends all the meetings in the US...And we often have visitors to the JVCI. Last week we had a chap from Canada and we had a very useful discussion of the HPV policy of Canada. The German and Dutch often attend. There is rather a lot of cross communication about policy between different bodies.”

The UK has the potential to reward good immunization practices. Incentives for immunizations, as Hall says discusses, “comes to another difference between the two [systems]. Primary care practitioners...are private contractors, but their money comes from the government and it’s based on the number of patients on their books, not patients they see, but population. If
they kept everyone perfectly healthy and never had to see any patient, they would be paid the same money, but do absolutely no work. So it is a very good inducement to keep people healthy... But they get bonuses for different things. One of them is that they get quite a worthwhile-having bonus if 90% of their children are completely vaccinated with all the immunizations by the age of two. So it's actually better than the US policy where you may have quite good coverage because of school-entry laws, but it may not be very timely. Whereas by targeting the reward earlier in life you get more timely vaccinations. That mechanism has to be thought about with any new vaccine—whether you build into it some kind of reward to whoever is going to deliver it for attaining high coverage." Hall concludes that, "fundamentally the vast majority of people agree to vaccination...there are two main obstructions. One is the people that are profoundly anti-vaccine and they are misguided and ill-informed. I think that is true. The second barrier is the vaccinator who is not fully committed to getting people vaccinated. So if you can induce them financially to be committed, then you can increase coverage...So the reason you sit on a vaccination committee is because you believe there is a public health benefit to be done through vaccinations."

Anti-vaccine sentiments in general and "morality" arguments in particular

Many experts agreed that the research statistics support the widespread vaccination of young girls against HPV. However, efforts to do so have met with opposition from American and British conservative groups and some parents, who worry that vaccination might encourage premarital sexual activity. This opposition on moral or "family values" grounds appears larger in the US than the UK. "That's more of a political question, of course," says Dr. Jennifer Wu, an obstetrician/gynecologist at Lenox Hill Hospital in New York City. "One thing that we do need to think about, however, is that we already vaccinate [girls] against hepatitis B—it's a universal vaccine for children. And hepatitis B is also a sexually transmitted disease." "We're certainly not saying, 'Go out and have sex now that you have the vaccine,'" Wu states, "We are just
thinking that, 'OK, these women may or may not have more than one sexual partner, and this might help protect them.'

"That is not completely new, you know, Hepatitis B is an STI and we have a vaccine. There were issues with the introduction of the hepatitis B vaccine as well. That was a number of years ago so it was a different place and different time," ACIP’s Gilsdorf notes. And added, "I do not think it was recognized completely, the public just did not tune into it then. One of the most compelling reasons to prevent hepatitis B infection is to reduce the hepatoma, the cancers that are the result of hepatitis B infection."

NWHN’s Allina believes the discussion about the "morality" of the vaccine has added to the controversy and skepticism. “There are certainly people who are resistant to immediately adopting the vaccine. One concern is that it will lead to adolescent promiscuity, give girls the sense that premarital sex is being condoned, you know by making sex safer, making it more appealing...I do not think this is the basis on which girls decide whether or not they want to have sex, but there are people who are worried about that. Then you also have the people who are concerned about safety of a new product where there are a lot of unknowns."

Allina surmises that “If the vaccination is given the way other vaccinations are given, it will not have that effect because girls will not even really have an in-depth discussion about HPV with their clinicians. They will just know they are being protected against another disease."

Some observers of the debate forecast the moral issues coloring the potential health and preventive medicine aspects of the HPV vaccine. This source of opposition could lead to decreased immunization success. ACOG’s Goldstein notes, “I think that, if there is a very strong religious, pro-abstinence group that lobbies at the state level, that could certainly interfere with state mandates...because they sort of win the debate on it. [A]nyone who agrees with this message would probably not get vaccinated...It could decrease vaccination rates. But I think, based on the various studies out there, that the majority of parents are saying that they will get their daughters vaccinated. So that implies that they don't really agree with what the
pro-abstinence or religious groups are saying about it promoting promiscuity and that they accept that the research out there that says this won't increase promiscuity."

"Data in the US show that about 25% of 15-year-old boys and girls have had sexual intercourse," says Markowitz, of the CDC, "so we certainly would want to get the vaccine into boys and girls before they begin sexual activity at that age." As noted earlier according to the CDC, more than half of sexually active people have had HPV at some point in their lives. "The CDC put out some research showing that the HPV vaccine isn't likely to lead to promiscuity. They talked about sexual risk-taking behavior being associated with many different things—and that fear of an STD is not a major motivation for abstinence. So... it is unlikely to lead to those things, but they are serious concerns," Goldstein with ACOG comments.

The CDC's Markowitz adds, "Since most people do become sexually active at some point in their lives, parents who opt to get kids the vaccine should explain to their children that they will need the vaccine to protect them when they are adults. Clinical trials show that the vaccine produces a good antibody response in early adolescence, therefore it may be a good time to get children vaccinated."99

The ACIP's Gilsdorf comments, "I think there are many [political] elements to this. I think that the pro-abstinence sentiment is more visible perhaps than it ever has been before. I think that the anti-vaccine in general sentiment has been organized... I think the internet has allowed some of that to occur. There are many people who are against all vaccines no matter what. They are also raising a lot of issues about this vaccine." She continues, "People have many issues, distrust in the medical system in general. The general public, it seems, and this has been documented in studies, is very suspicious of government, of big business, of many things but they love their doctor and they trust their doctor. I will tell you, this is a really important thing for you and your medical students to understand; the most valuable thing we have is the trust of our patients and when we lose that we are done, and I am very fearful of our patients losing their trust in their physicians."
These anti-vaccine sentiments and "morality" arguments are not as prevalent in the UK as they have been in the US. Officials believe what is occurring arises for similar reasons, especially because the vaccine protects against an STI and not just a casually communicable disease. "In America, where the poles are even more extreme, it is a huge issue. It happens here in the UK. It's like a microcosm of the US. It is, however, never as violent, never as extreme, the opinions, and they don't tend to be barriers," Kerridge of MSI says, comparing the two systems. NHS's Hicks comments, "The right wing, of course—we don't have quite the moral, religious right wing you have in the States. But, we do have campaigners. They say, as they said with the oral contraceptive pill, that vaccination is an encouragement to have sex, and have sex early, and they're talking about under-aged sex and side effects. And trying to knock back the progression, of, well, what is Gardasil at the moment, but it will have a rival..."

NHS's Hicks says "Now if this were a vaccination against bird flu, we wouldn't be having these arguments. We wouldn't be bothering about costs or be concerned about long-term effects. It's the fact that we are talking about an STI, really, that's brought in this moral dimension that is clouding the issue...I think so. We recognize that there is an argument, but the NHS starts up from the premise that treatment is free to everybody at the point of need. Such a simple statement does not really take into account, or want to recognize, whether that person has paid into our system, is an illegal immigrant, has a moral position, is gay, is whatever. It is just an overarching statement. So, the very principle of the NHS kind of, not ignores—doesn't feel that moral positions carry the final say."

A couple of the UK opinion leaders emphasized the role of the media as influential in shaping the anti-vaccine feelings. "It's media led," said MSI's Kerridge. "We've got a very strong and powerful right wing media in this country. Organizations like MSI and everything we stand for at MSI is an anathema to them. Their view on things like Gardasil is that what you're doing is giving young girls the green light at 12 or 13. That if you even contemplate offering something, for example, some schools allow school nurses to dispense emergency
contraception. Anything like that, their view is up until the age of consent at 16, that everything should be sacrosanct. And if you do anything to address any aspect of pre-16 sexuality, you are encouraging sex among the pre-16s. They don’t seem to grasp the notion that it’s like trying to shut the stable gate after the horse has bolted. We all know that young people are having sex earlier and maturing earlier. There is not a lot we can do about that, other than give them information, protect them, and help them to deal with it. As an organization, we are not here to moralize or place judgment on anyone. So this issue is an element that that side of the press will frown on with Gardasil. For example, if the NHS bought into it and offered it as standard to every girl, if that day should ever come, then certain courses of the media and the public that share their views will be outraged. So it’s an area where there is always constant debate. It makes achieving things that much more difficult for the NHS and organizations like ourselves. So there is that social element that is around anything to do with pre-16 girls having sex.”

The JCVI chair Hall may see less media interest than does Kerridge: “I think that plays a larger role in the US, I don’t know how much is publicly driven and how much is media driven, but it has been picked up in the UK media. In general the JCVI commissions social research, and one of the things was a survey of public opinion. So we do qualitative research as well as modeling. And it’s certainly not a wide-spread concern here. I personally don’t think it is in the US either. And I think the media here are less likely to get very excited about it, fortunately. We don’t see that as a major issue. It could be an issue in terms of whether you go for primary versus secondary school children. I think it would be much more difficult for parents to perceive their 10-11-12 year-old pre-pubescent children as sexually active as a 13 year-old. It may psychologically play a role in which of those you choose... In terms of [potential] negative outcomes with the vaccine — decreased condom use, increased STI transmission, and increased unwanted pregnancies — it is a concern that has been raised. We have the worst teenage pregnancy rate in Europe. We are not exactly worried about it increasing the rate—we want [the rate] to come down. My personal belief is that we should be looking at the HPV
vaccine as an opportunity to deliver an educational package that could be embedded as part of an adolescent health program, and certainly relating it to sex education. Again this is a reason why younger children may be less favored than older children. I think the sex education program is pretty rudimentary in primary schools compared to what goes on in secondary schools, about life risks, etc... I think that increasing knowledge and awareness in general modifies their risky behavior downwards rather than upwards. And I think the idea that you could deny somebody something which will prevent any disease, but particularly a fatal one, because oh, they might increase their risks is a particularly bizarre argument. I just cannot see that at all.

**Paying for the vaccine**

The issue of the expense of the series of three shots has generated a lot of discussion in both systems, especially when the vaccine has been recommended as standard of care in the US and has the potential to be recommended to all British females in the approved age range.

In the US, pediatrician Cross argues, "It is not inexpensive. If it were free I would say a fair portion of the female population would get vaccinated. I think we have done a good job of advertising it. Even the controversies in Texas [over what motivated Governor Perry's support of a vaccination mandate] and other places have, in fact, advertised the vaccine. But the expense is huge, $160 a throw [meaning a single injection of the required three]. That is going to be a significant deterrent. Now, I believe that in North Carolina most insurance companies are covering it and the State vaccine program is covering it for people under 18 who qualify."

Merck calculated the price based on the money the vaccine will save the entire health care system. The CDC endorsed the price, as it does with other vaccines. "We based the price on a number of factors, most importantly the value Gardasil brings to individuals and society," says Jennifer Allen, a spokesperson for Merck. "HPV-related diseases cost the US health care system about $5 billion every year, and we took that into consideration." Although Merck
would not make sales projections public, population data show that the vaccine would gross
more than $11 billion if all women 11 to 26 in the US were vaccinated.\textsuperscript{100}

The HPV vaccine is the most expensive routine vaccine in the US; in contrast, many
childhood vaccines combine several immunizations in a single shot for $20 to $30 a dose. For
about $1,200 an American child (more specifically, her parents) can buy protection against 14
dangerous diseases, for an average of $87 per disease.\textsuperscript{100}

Additional financial support for childhood immunization comes from the national US
program Vaccines for Children (VFC) Program that provides vaccines recommended by the
CDC's ACIP for free until 18 years old. Since 1994, the VFC program has provided free
vaccines to children who are Medicaid-eligible, uninsured, Native American, and to
underinsured children who visit Federally Qualified or Rural Health Centers.\textsuperscript{101} Merck makes 9
of the 15 vaccines for children that the ACIP recommends—more than does any other company.
The company provides the pediatric vaccines to the VFC program at "significantly discounted
prices."\textsuperscript{102}

This program does not include low income, uninsured females 19-26. Very limited public
funding is available in the US to provide vaccines to uninsured adults. As a result Merck has
created the Merck Vaccine Patient Assistance Program. Merck promotes this as a private and
confidential program that provides vaccines free of charge to "eligible adults, primarily the
uninsured who, without our assistance, could not afford needed Merck vaccines."\textsuperscript{102} However,
Markowitz comments that "One of the problems with that [Merck's Vaccine Assistance Program]
right now, I understand, is usage mainly in private clinics, not public clinics. So that has
somewhat limited the use of that program... It seems the opposite of where it would be useful."

In the UK, the Treasury has the final say, since it funds the NHS, but as a single national
supplier, the NHS is able to negotiate price. "We should be clear about that. Unlike the US,
here what will happen is, if the vaccine is recommended by the JCVI for universal use and that
recommendation is adopted by the government, then the vaccine supplies are purchased centrally, at a single point, which allows you to negotiate the better price," Hall reports.

The vaccine is available only privately in the UK at present, increasing concern about health disparities. MSI's Kerridge comments, "I think that probably most mothers want to do the best by their child and they tend to be quite sensible about things like this. I think the big stopping block at the moment is the money. It is a lot for the average family on a budget. So, it will be embraced more by the upper levels and socially mobile, not the working-class people on fixed budgets. It is something that polarizes people."

According to some UK officials the price of the vaccine is a barrier to national use, since historically in Britain reproductive health care is not as well funded as are other areas. "[T]he whole side of NHS that deals with GU clinics and sexual health is the 'poor relation.' And as a result gets funding cut and continues to face cuts." Kerridge says. He continues, "The PCTs, Primary Care Trusts, have far more control now over their budgets and the decisions they make. We hear anticdottally, time and again how money that perhaps should be set aside for a particular endeavor is being shifted over because they can live with a few more people living with gonorrhea in the area, whereas they've got to get their cancer treatments and their targets for that down. That takes priority and the budgets are finite." MSI's Baldock continues, "It is...The idea of 'you brought this on yourself.' And it's not an emergent situation." Kerridge says, "It is a big problem. And this vaccine will be way down on the list of NHS priorities." Baldock concludes, "But we see the vaccine in a totally different light than maybe the general public. And that is that everybody should have it, regardless of cost... Whether the new vaccine [Cervarix] will come in and compete and bring the whole cost down, we just don't know.

Public and clinician education

Along side the actual vaccine supply funding is the need to educate and teach both the public and their doctors about HPV and the vaccine for it, calling for additional expenditures.
Both countries’ officials are grappling with this complex need. Both the CDC & ACOG agree on the need for more public awareness and education. “In the best of all possible worlds the introduction of the vaccine will also be an opportunity to educate the public about HPV itself” says the NWHN’s Allina states. ACIP’s Gilsdorf points out that “[m]uch of the educational campaign has already been provided by Merck because it is obviously in their best interest to have the public know about this vaccine. They have definitely been providing a lot of the information that is available. Is that enough? I don’t think so. Is it well balanced? Not necessarily. So, then we get down to who can best provide the most accurate information. The primary physicians? They don’t have time to sit and explain all this to their patients in their practices. They have 10 minutes, remember, to see their patients. The local health departments? Most local and state health departments are seriously, seriously, seriously under funded. So where are the resources going to come. Obviously good education needs to be available to the public, where is it going to come from? Who is going to pay for it? That is a huge question.”

ACIP’s Gilsdorf believes that the presence of the vaccine has increased awareness about the virus, and that the awareness has extended to clinicians as well. She says, “I think they are really seeking a lot of information. Prior to the introduction of this vaccine, many, many, many people knew nothing about cervical cancer and certainly did not realize that this is this virus that causes this cancer. The public information about cervical cancer was extremely limited and even among healthcare professionals. Pediatricians for example, do not deal with cervical cancer. We do not routinely do Pap smears... so there is just a lack of information about the virus and about the disease. That has to be a part of the whole process, making sure that the public and that the health care community understands the disease and the vaccine, and how best to use the vaccine to prevent the disease.”

UNC pediatrician Cross points out that HPV is “one of many diseases, probably the one that people have been least aware of and least concerned about and least aware of the
prevalence. So I think that there was a period of time, until quite recently, when I think many young people thought that the only significant STD was HIV and all their behavior focused around what they had learned about preventing HIV. I think that accounts for what we are now considering, but I do not think we have proven, to be the cause of the epidemic of oral sex in middle school. I think it is a very responsible, logical direction in which hormonally driven teenagers have chosen a behavior that they have been taught was a low risk for what was the major threat, HIV. Without recognizing that this was, in fact, an increased threat of herpes, which now leaves us totally confused as to whether it is type I or type II and belongs in the mouth or the genitals. All that is a reaction to our HIV education. So now all of a sudden kids are beginning to realize, Whoa! Herpes is a big deal. It is 32 times more common than HIV. I do not think that anybody has paid a whole lot of attention to HPV, which is up there at the same level of commonness as herpes. Even...the guys would think, well this is a problem for my partner but it is not a problem for me, whereas HIV was a problem for everybody.”

At the UK’s MSI, where the vaccine is currently available for a fee, clinicians spend a long time teaching their patients about HPV. Their time commitment only reinforces the need for more national, public education about the vaccine. Baldock says “Certainly when we discuss the vaccine, we try not to scare them to think, ‘I’ve got HPV. I’ll get cancer.’ And we’ve tried to explain about warts. It’s a conversation we try to have with all our clients. Certainly if they have warts, they don’t know enough about warts to associate it with HPV or anything else. A lot of them don’t think about them as warts—more like skin tags. So it’s an educational thing when people come into see us and we have to explain it very nicely. We book them for health screening appointments [with varying content]...[T]hey usually don’t get less than 40 minutes” [of time with an educator during their clinic visit].

“I think, as with any public health message, we need to get more information out there. We need to increase funding for things like family planning and STD treatment and prevention efforts, for screening pap testing. And certainly in terms of decreasing sexual risk-taking
behavior, we need to increase funding for comprehensive sexuality education. But I don't think it necessarily needs to be tied into the HPV vaccine. And yes, we need to make it clear that the HPV vaccine only vaccinates against four types of the HPV virus and that Pap testing is still very important because there are other viruses out there. It needs to be made clear that the vaccine is not against any other STDs... So education is critical," wraps up ACOG's Goldstein.

Implications of the vaccine for cervical cancer screening

Will women stop getting Pap smears after the HPV vaccine becomes widely available? Kerridge notes, "I think the other big problem, besides cost, is that the vaccine will never replace cervical cancer screening because it only protects against certain strains and you can still get cervical cancer. So, if it were something that would make cervical screening obsolete, then there is a clear cost benefit to doing it. But its not going to do that is it? There will still be regular 3 and 5 year screening [in the UK]." Baldock echoes the concern: "It will have to be very clear that this vaccine won’t take the place of screening. [To think that it will] is a really dangerous risk."

The NWHN's Allina also raises the point: "It is a very complicated message to explain this protects against strains of the virus that cause cervical cancer, but not against all the strains that cause cervical cancer. If girls and women do not understand that they are not 100% protected from HPV causing cervical cancer, then they may stop getting Pap smears, and that will be a very serious downside to the vaccine... We have done a really good job in reducing cervical cancer incidence in this country by making sure that women were able to get Pap smears and were getting them... we could easily end up going in the wrong direction."

Allina also raises the financial consequences of absorbing the HPV vaccine into the cervical cancer screening budget: "[W]ill women, girls, and clinicians understand it? But also from the perspective of need[ing] to continue to invest in our screening programs. If states, for example, were to shift the money that they are spending on cervical cancer screening and use it
to pay for vaccines, they could end up with worse cervical cancer rates than they have now. They need to keep doing both."

Commercial interests and product hype can lead to overly high expectations. The ACIP’s Gilsdorf gives the example with stem cells and gene therapy. She wants the public health message to be clear that the vaccine cannot erase cervical cancer. "You may or may not remember all the stuff that went on about gene therapy and how gene therapy was going to...Unfortunately, the scientific community raised the expectations of the public beyond what it was possible to deliver. This vaccine is not going to prevent all cervical cancer. However, I have participated in several forums where people will say, especially the politicians, that we are going to erase cervical cancer from the United States, and I say, 'No you’re not, not with this vaccine you’re not.' You need to understand the limitations as well as the benefits."

Another public health fear is that condom use will go down once people think they are protected from HPV through vaccination. However, both UK and US officials are not worried about that concern. Cross says, "So, I do not think it is going to discourage people from using condoms. I think they are convinced about the condom value for pregnancy prevention and HIV prevention. When I quiz my patients about what they should be doing to be safe when they are having sex, or being safe as possible, I always try and point out that there is no such thing as safe sex. I am very much at the very liberal end of the scale, but I am very quick to point out that the only truly safe method of prevention is abstinence and I strongly encourage abstinence. I also recognize that my advice is not always going to be taken so I need to go a step further than that...I usually talk a lot more about herpes and HPV than I do about HIV just because that is where the deficit in knowledge is. My teenage population of patients is skewed a bit towards the male end. Some of the girls leave me when they are ten and modest. I point out to the boys what a huge risk pregnancy is for them and a lot of aspects about that they have never thought about."
Males Included?

Whether males should be vaccinated is an important but somewhat overlooked part of the puzzle of eradicating oncogenic HPV strains. US and UK key informants had slightly different takes on the question of immunizing males. In the US, the policymakers focused more on the fact that the science is not there to back efficacy in the male population. Interestingly, in the UK, the vaccine is licensed for use in both sexes, with a tighter age limit, 9 to 15 years, for males. What about the approval process enabled the UK to recommend in favor of vaccinating males, while the US FDA says the evidence for vaccinating boys is not adequate?

Both the CDC and ACOG take the position that more research needs to be done before any decision can be made. ACOG’s Goldstein says, “The other question that I’ve seen come up about boys is the issue of cost-effectiveness. Really the big bang for the HPV vaccine is preventing cervical cancer and that has a higher prevalence than what the boys get, like the penile cancers, throat cancers. Although it terms of genital warts, certainly, it could be helpful in that arena. But in terms of cost-effectiveness you have to look more at cervical cancer. If all the girls, theoretically, get vaccinated against HPV then all the boys may not need to. So in terms of a cost-effectiveness argument it may not be cost-effective to vaccinate boys because the vaccine is so expensive. But there’s no data out there right now, so it is hard to say if it will or won’t be cost-effective in boys—or even work in boys. That is a big ‘to be determined’ question and a lot of people are asking that.”

The CDC, ACOG, and the NWHN all are in agreement that until more data is available for vaccine use in males, there is no point in promoting the health benefits or the sense of shared responsibility of sexual risk between the sexes. Allina: “When Merck went to the FDA for approval the first time around they asked for approval for boys and girls. The FDA said, well you have not done the study in boys yet and we cannot approve it until we have data showing that it works for them. So the company said that they had started studies in boys and they were going to continue them, but until they have collected [those] data and submitted [them] to the
agency they will not have approval to vaccinate boys. While some boys might get vaccinated before that happens, it is not going to be on a large scale. At the point at which data have been submitted to the agency and reviewed, if it looks as strong as the data for girls we would absolutely want to see it approved for use in boys. We would want to see it adopted by clinicians for use in boys because we, as a philosophical principle, do not want to see girls burdened with the responsibility for protecting both themselves and their partners from disease. That is a responsibility that should be shared equally, but we are not going to be out there advocating for vaccinating boys with a product that has not been tested in them, that would just be unethical.”

Cross agrees and thinks the issue should be explored further. “I am not sure how common anal papilloma virus carcinomas are and the other consequences so we need to research the value of the vaccine in that population. That, to me, is something that we should move forward on. It is a niche population, if you will, but one that would still be of value. Again, part of the pharmaceutical industry’s motivation is to get their drugs to be used by the largest number of people and they tend to not spend the additional money that it might take to cover a small group that would benefit if their likelihood of market payback is small. The profit margin to study this, in less than 5% of the population, is not going to be worth the cost of that; whereas to study its efficacy in 50% of the population has a much larger potential payback. Again, my disapproval of the motivation of the pharmaceutical industry… I am not sure why, I mean, you would think that at face value that the pharmaceutical industry would love to have that other 50% of the population in their market share. So I am not sure whether they are aggressively pursuing that in this country and have run up against roadblocks or whether they made a political decision that this would further ignite the abstinence crowd and maybe block it for everybody, or why they are behaving the way they are.”

By comparison, UK officials were more concerned about the lack of equality between the two sexes. Hicks says, “Men are being excluded. And I don’t know any vaccine where you can
do that... It is only going to work if it is applied through either sex.” However, it may be a hard sell to pre-teen and teenage boys. According to the MSI leaders, though it is legal to vaccinate males, they have not vaccinated a single one. Kerridge notes, “That doesn’t surprise me. The ultimate objective is to protect women. I know that HPV infection can affect males, but...I think it is fair to say to a 14-15 year old girl, ‘go and have your HPV jabs and you’ll be fine.’ It’s a hard sell to a teenage boy, ‘Go and get these jabs, it will protect your wife down the road.’ So I think there is that, which is having a bit of a knock on the success of the vaccine.”

Hall reports on the British approval for both sexes. “The modeling so far suggests if you vaccinate males and females, you double the cost. And the marginal benefit of control of HPV is only 10-15% on the models that we have seen; therefore you don’t have to be an economist to know that it’s not going to be cost-effective really. That raises important issues about subgroups of the male population that are at high risk for developing HPV induced cancer and whether there is a strategy by which we can protect them. In terms of equity, it would only seem right that it’s available through government funding to them as well as to women. But it’s clearly never going to be through universal vaccination. Among the interesting things will be to actually see the impact of a national HPV campaign in women alone on the epidemiology of HPV in general. We very well may see a major herd-effect on subgroups such as men who primarily have sex with men. It’s not clear that the carriers of those men will act as a sufficient reservoir. So it will be an interesting issue.”

**Implementing HPV Vaccination Programs**

The US has consensus guidelines for vaccine use in place and implementation has begun. The CDC and ACOG foresee widespread vaccine adoption. According to ACOG’s Goldstein, “My sense is that once the CDC releases guidelines pediatricians who are used to vaccinating will jump right on. If they are new to vaccination then it will take some time until they can follow the guidelines.”
The CDC's Markowitz believes some aspects of the guidelines will be followed more closely than others. "I think we all agree on routine vaccination of 11-12 year olds, and I think that that recommendation is being implemented in most states right now. So I think that recommendation along with the catch-up though age 18 will be adopted. Those children are covered under the Vaccines for Children Program and are provided vaccines free of charge to eligible children in all states. So I think that part of the recommendation will be implemented. I think it will become used routinely in the US. And I think it is already incorporated into a lot of our routine vaccine schedules that we publish here—the ACIP schedules. The American Academy of Pediatrics along with the ACIP are the most important bodies because most of the people that administer vaccines in this country are pediatricians. And so, the American Academy of Family Practice has the same recommendation. So a lot of groups have come up with similar recommendations. Recommendations by professional bodies are very important. And then financing is important—those are the two things that I think are very important for getting the vaccine out."

As a pediatrician already providing the vaccine Cross comments, "I have been a slow adopter of several other vaccines so that is my general starting point." He ironically adds, "The only drugs, and this includes vaccines, that do not have side effects are new drugs and that is why I like to use old drugs because I know what I am dealing with. So, having said all that, I am offering and encouraging the HPV vaccine. Despite my general philosophy of being a late adopter, this one seems like a pretty safe vaccine with a high likelihood of being protective of a potentially fatal condition."

In addition to the guidelines being in place in the US, it appears that the general public is very interested in the vaccine. Cross said "This is a vaccine, more so than meningitis for example, where I have gotten mothers or even patients to contact me because they want to get it. So I think there is a perception out there that this is the smart thing to do, worth whatever risks turn out to be there."
In fact, data suggest that the majority of parents will get daughters vaccinated.\textsuperscript{103} NWHN’s Allina summarizes that the vaccine will “generally [be] adopted quite broadly, but that it takes some time. Medical practice does not change overnight and it will be interesting to see how it plays out because in some ways you might think the change would happen more quickly because there is so much media attention to it that you would think people will hear about it sooner.”

In the UK, for a variety of reasons, interest in the vaccine has been slower. The UK prohibits DTCA advertising, and the JCVI had not, until June 2007, decided whether to recommend that the NHS adopt the vaccine. Officials believe that interest in the vaccine is now growing, with the Department of Health and MSI receiving more calls about the vaccine.

The first newspaper article about the HPV vaccine to be published in a free paper handed out at the London Tube stations occurred in May 2007. MSI’s Kerridge reports, “Today it was really weird, Corinne’s coming and it’s on the front page of \textit{Metro}, there is the HPV vaccine. If you go by a tube station, you will find one or pick it up on the train.” Leatherman observes that “\textit{Metro} has huge circulation because everyone picks it up. So lots of people will read it and be aware of it. So in the UK they [pharmaceutical companies can't advertise]. But getting something in \textit{Metro} is more effective, probably even better than advertising. It has a wide readership of the right age group because people who ride the tubes are the teenagers and up to about 35.”

From the perspective of MSI, Baldock notes, “It was very slow in the beginning, but it has picked up...We’ve had quite a lot of inquiries over the phone about it. The money itself puts some people off, it’s expensive. But if my daughter were in that age group I would certainly get her vaccinated...ultimately I think they [the NHS] were waiting, at one point, for the next vaccine to come out. And they were going to do that because it was given to a wider age range.”

The NHS’ Hicks says “Specifically on introducing a HPV vaccination program, the Department of Health has sought the views of parents about appropriate ages and venues for
vaccination against HPV. The research indicated that most parents had not heard of the HPV and were not aware of the role of HPV in causing cervical cancer. There were concerns about offering a vaccine that protects against a sexually transmitted infection and that the vaccine should be offered at an older age, in conjunction with a sexual education program. Hicks acknowledged that work needs to take place now in order to raise awareness of the vaccine, including among providers, and of HPV as a cause of cervical cancer, prior to any introduction of the vaccination program. “The Department has worked extensively with school nurses in previous immunization campaigns, much of the success of which can be attributed to the excellent implementation work in school environments,” said Hicks.

On June 20, 2007 the UK provisionally agreed to begin a program of HPV vaccination to prevent cervical cancer for girls starting secondary school aged 12-13. The Department of Health said that routine vaccination of girls could start as early as autumn 2008, though details of the program will be finalized over the next few months, following further advice from JCVI and discussions with the NHS.

Conclusion: Different Roads to HPV Vaccination

Randomized controlled trials have shown that both HPV vaccines, Merck’s Gardasil and GlaxoSmithKline’s Cervarix, are safe and highly effective in preventing persistent infection and lesions caused by HPV 16 and 18—the types responsible for 70% of cervical cancers worldwide. Determining an effective vaccination strategy is now the most pressing issue facing clinicians, parents, public health officials, and policymakers.

Awareness and education of the risk factors associated with cervical cancer and HPV infection are major women’s health and adolescent health issues. The US and more recently the UK have moved toward population-wide HPV immunization.

Both systems are now committed to HPV vaccination at some level, though each system will pursue its own route to immunization. As they begin their immunization programs, each
system must continue to seek answers to several questions. What are the vaccines' characteristics long-term, that is, in terms of duration of protection and degree of protection? What is the appropriate use and level of efficacy of HPV vaccine in males? What implications will arise from the use of two different vaccines within the same populations? When can we expect to see more and better epidemiologic and natural history of disease data to support HPV models, including models of other important HPV-related diseases such as vulvar and vaginal neoplasias and cancers, recurrent respiratory papillomatosis, research to model HPV types' interaction and cross protection, and models to reflect the indirect costs of HPV-related disease.

The future for the HPV vaccine and its implementation is extremely complex. The very recent British announcement to add HPV vaccination to the National Immunisation Programme is great news for Merck, whose Gardasil, is the only licensed “jab” in Europe for the prevention of cervical cancer. GlaxoSmithKline's vaccine, Cervarix, is currently under review by EU regulators.92

Once both vaccines are available, current or in-development guidelines will need to be reconsidered, since the vaccines are neither synergistic complements, protecting against the same strains of HPV, nor replacements for each other. The CDC’s Markowitz speculates, “With both available, what will the recommendation be? Will there be a reference for one or the other? How much value is there to the HPV 6 and 11 components? We need to look at the [health] outcomes that are caused by 6 and 11. And all those things are going to be considered. In the past there have been more than one vaccine for the same infection on the market, and usually advisory committees do not express a preference for one vaccine or the other. In this situation the two vaccines on the market are going to be slightly different. So that is the issue that the committee is going to now be addressing. It’s very complicated because it’s good to have more than one vaccine on the market for competition because of price, and because of capacity. It’s good to have more than one vaccine manufacturer. On the other hand it will cause some confusion—particularly if people value protection against things that can be
prevented by a vaccine against 6 and 11. That’s an issue that will be included, not just genital warts, but respiratory papillomatosis which is caused by 6 and 11. There are no data right now that says whether that outcome is protected against, but it is an outcome of HPV 6 and 11. It’s going to be a really complicated issue."

Kerridge of the UK MSI predicts that “the price will come down and the age range will increase. The new one [Cervarix], they are talking about the age almost going up to menopause.”

In the US, the state mandate discussion continues. The US Association of Immunization Managers (AIM) statement says, “School and child care immunization requirements must be used sparingly, approached cautiously, and considered only after an appropriate vaccine implementation period. This vaccine implementation period is critical to ensure that the necessary elements are in place to support a school requirement.”104 These elements include coverage for the vaccine in private health insurance plans, sufficient funding to purchase the vaccine, physician/provider support for the vaccine, public acceptance of the vaccine, stable and adequate vaccine supply, addition of vaccine to immunization information systems (registries), adequate data to assure vaccine safety, and significant uptake in the recommended population to reduce the compliance burden on the school system.

The extent of the US AIM imperatives for school immunization programs would seem to mitigate against HPV vaccination via schools, and would seem to be another challenge for supporters of state mandates. Even without school-based HPV immunization programs, in the US, as the UK is expecting to create, US state mandate discussions may still promote awareness of cervical cancer prevention and HPV infection, and may foster wider acceptance of vaccination. US state mandates are probably in abeyance for a while. If the US continues to keep an eye on the vaccine activity in the UK, however, the policy direction may change.

Another US obstacle to school-based immunization is the current restrictions on current federally supported and funded sexual education curricula to an abstinence only approach not
including information on condom use, birth control, or a discussion of STIs such as HPV. Should the current abstinence-only ideology give way to broader curricula, the discussion of the HPV vaccine may serve as a valuable educational opportunity for women and men about their reproductive health.

Different structural features have meant that the US could approve an HPV vaccine faster than did the UK; different constellations of political forces, however, may mean that the UK actually implements a national-level HPV vaccination program before the US does.

In the new HPV vaccine discussions, billions of dollars are at stake, millions of people may be spared from HPV infections, and thousands of women could be spared a diagnosis of cervical cancer every year. Many decisions have been made and many decisions are still in process. Only time will reveal if Merck, GlaxoSmithKline, the US, and UK health systems and their citizens made the right decisions.
Appendix 1: Elite Interview Respondents

I. US/UK Policy Analyst
Leatherman, Sheila, Professor, London School of Economics, University of Cambridge and the University of North Carolina at Chapel Hill and a member of the (US) Institute of Medicine. In-person interview conducted May 15, 2007. Chapel Hill, North Carolina.

II. US Interviews
Gilsdorf, Janet, MD, Centers for Disease Control, the Chair of the Advisory Committee on Immunization Practices HPV Vaccine Workgroup and the Director of Pediatric Infectious Diseases with the Department of Pediatrics and Communicable Diseases, University of Michigan. Phone interview conducted May 29, 2007. Chapel Hill, North Carolina.


Allian, Amy, National Women’s Health Network (NHWN), the Program and Policy Director, Washington, D.C. The NHWN is an advocacy group focused on developing and promoting critical analysis of women’s health issues in order to affect policy. Phone interview conducted June 6, 2007. Chapel Hill, North Carolina.

Cross, Alan, MD, Professor, the University of North Carolina at Chapel Hill School of Medicine, Social Medicine, Adolescent medicine, and Pediatrics, Director of the Center for Health Promotion and Disease Prevention. In-person interview conducted June 1, 2007. Chapel Hill, North Carolina.

III. UK Interviews
Hall, Andrew, MD, Professor, the London School of Hygiene and Tropical Medicine, Chair of the Joint Committee on Vaccination and Immunisations (JCVI), Chair of the Subcommittee on HPV Vaccine. In-person interview conducted May 10, 2007. London, England.

Hicks, David, MD, National Health Service Hospital Director and a member of the Royal College of Obstetricians and Gynaecologists (RCOG). In-person interview conducted May 8, 2007. London, England.

Kerridge, Tony, the Marie Stopes International (MSI), Senior Communications Manager-Press and Public Affairs. MSI is an international organization who promotes women’s reproductive rights and health care. In-person interview conducted May 10, 2007. London, England.


Appendix 2: The Structured, Open-ended Interview Protocol

I. Interview introductory script with embedding fact sheet and consent information:

United States and United Kingdom Comparative Health Policy and Drug Approval Process Analysis of the Adoption of the Human Papilloma Virus Vaccine. A Study by Corinne Epperly, at the University of North Carolina at Chapel Hill

Information Sheet

IRB Study # 07-0655
Principal Investigator: Corinne Epperly
UNC-Chapel Hill Department: Public Health Leadership Program

Faculty Advisor: Sue Tolleson-Rinehart PhD
UNC-Chapel Hill Department: UNC Center for Education and Research on Therapeutics and Departments of Public Health Leadership, Pediatrics, and Political Science

Advisor Phone #: (919) 843-9477
Advisor e-mail: suetr@unc.edu

Study Contact telephone number: (919) 923-3120
Study Contact email: corinne_epperly@med.unc.edu

Introductory script:

Hello, I am Corinne Epperly. Thank you so much for meeting with me[telephone interview]. I am a medical student at The University of North Carolina at Chapel Hill. I am conducting research to fulfill the requirements of the Master's of Public Health degree in the Health Care & Prevention program.

I have asked to interview you because of your knowledge of cervical cancer screening and prevention programs. I am talking to people like you in both the United States and the United Kingdom. I'm particularly interested in how people are approaching the potential use of human papilloma virus (HPV) vaccines.

I will be asking you questions about the adoption and dissemination of the HPV vaccine. I am interested in getting your opinion as a policy maker and/or elite stakeholders/key informants who has contributed to or is establishing policy for approval[US interviews]/potential approval [United Kingdom interviews] of any present or future HPV vaccines.

My faculty adviser is Dr. Sue Tolleson-Rinehart, who is a faculty member of the UNC Schools of Public Health and Medicine. We hope this study will help people better understand how effective policy for the use of HPV vaccines can be made.

The interview has several questions, all in open-ended format. The interview should last anywhere from 20 minutes to one hour, depending on the availability of your time and what you want to tell me. I would like to record this interview on a digital voice recorder to make

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absolutely sure that I have the most accurate record of your comments. I will not record this
interview without your permission. If you do grant permission for this conversation to be
recorded on cassette, you have the right to revoke recording permission and/or end the
interview at any time. I will transcribe the interview, and I will give you a copy of the transcript.

The audiotapes made of the interview will be kept in a locked cabinet and destroyed after the
transcript is made. Transcripts will be encoded on my computer and the computer of my faculty
advisor, Dr. Tolleson-Rinehart, and they will be controlled by a password. only accessible with
my password. No one else has this password. You will be able to review the transcript and
discuss revisions with me at the follow-up.

Your participation in this study is completely voluntary. Your choice of whether or not to
participate will not influence your future relations with the University of North Carolina at Chapel
Hill. If you decide to participate, you are free to withdraw your consent and to stop your
participation at any time without penalty. At any particular point in the interview, you may refuse
to answer any particular question or stop participation altogether.

If you have any questions about the research now, please ask. If you have questions later about
the research, you may contact me by phone at (919)923-3120 or by e-mail at
corinne_epperly@med.unc.edu.

Dr. Tolleson-Rinehart and I intend to try to publish the results of this project, and will be glad to
make findings available to you. For any questions about the study, please send a message to
medgradsurvey@unc.edu or call (919)843-9477.

Risks and Benefits: I know of no risk to you from completing this survey. While you may not
benefit personally from completing this survey, I believe that you will be helping the larger health
care community by enabling us to understand how policies associated with preventing cervical
cancer can be made most effective.

Before we continue, please check[in person]/agree to[telephone interview] either or both of the
boxes below.

☐ I AGREE to having this interview tape recorded with a digital voice recorder.

☐ I GIVE PERMISSION for the following information to be included in publications
resulting from this study:

☐ my name ☐ my title ☐ direct quotes from this interview

Name of Participant (please print) Date

Thank you for your help with my project! Now we are ready to begin.
II. Interview Questions

A. US/UK Policy Analyst

1. How do you see the HPV vaccine fitting into current US and UK health care and women's health efforts?

2. How do you see the HPV vaccine getting implemented in the US? What about the UK? Do you anticipate approval there?

3. What are some of the greatest differences in the political context surrounding the HPV vaccine in the US and the UK?

4. Evaluation often points to some policy failure. Would deliberately not crafting evaluation strategies for policies be a viable political option? (And if you don't evaluate, you can't be accused of having failed?)

5. People in the different policy networks are not just on different sides—but really in different worlds. In your judgment, which actors stand to gain or lose the most from HPV vaccine. Who stands to gain or lose from HPV vaccinations?

6. What are alternative ways to look at the "business case," the financial implications, for HPV vaccination in the US and the UK? Do you believe the vaccine can yield a return on investment?

7. Cost-effectiveness is a large part of NICE's approval process, as opposed to the FDA's approval process of new drugs, how do you see cost affecting the process?

8. Pharmaceutical direct-to-consumer advertising is legal in the US, not in the UK. Do you think Merck's advertising campaign is informative, helpful, and educational or an emotional promotion, creating a sense of urgency, and confusing for the American health care consumer? Is it a solution in search of a bigger problem?

Thank you so very much for your time and thoughts! Do you have any additional questions or comments? Thank you again!

B. US Interviews

1. The FDA approved Gardasil for women 9 to 26 years of age. The American College of Obstetricians and Gynecologists and the Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices (ACIP) are recommending its use in girls 11-12 years old. How broadly do you think these guidelines – for immunization of 11 and 12 year old girls -- will be adopted?

2. In your view, are primary care providers following the news about various efforts to mandate the use of the vaccine? Do you think this news is affecting their view of the vaccine in any way?

3. And how would you say U.S. consumers – especially parents – are responding to the availability of Gardasil?

4. Now I'd like to ask you your perspective on some of the issues people have been airing both pro and con about Gardasil use.
4.a. First, a campaign to convince parents to allow their pre-teen and teenage daughters to be vaccinated against a sexually transmitted infection (STI) could run into opposition from some pro-abstinence and religious groups, who fear that the vaccine may promote promiscuity. In your view, how would such opposition affect efforts to implement vaccine use?

4.b. What potential public misconceptions about the HPV vaccine do you see on the horizon? [Probe with specific questions about misconception that Gardasil will prevent STIs only if the person doesn’t volunteer.]

4.c. Some people are concerned that people might have other misconceptions or false sense of reassurance about what Gardasil can and can’t do. Do you see other such problems on the horizon? [Probe about condom use if not volunteered.]

4.d. Finally, in your view, how serious ought we to be about whether Gardasil use might be associated with increased unplanned pregnancies, increased abortions, increased rates of other types of HPV, and increased rates of other STIs, including HIV? Would you say these are serious concerns, or not so serious? And what should the health system and the public health community do, starting now, to address any of these concerns?

5. We’re on the last question! Whether boys should be vaccinated is still an open question, as you know. Including boys is likely to be important for the development of group immunity but male disease is rare and, to date, there have been no studies that demonstrate that men can be protected. But Gardasil might have some advantages for men as well, such as in the prevention of genital warts and the prevention of anal cancers. Looking down the road, how likely -- or not -- do you think it is that guidelines will include vaccinating boys? [Probe as needed]

Thank you so very much for your time and thoughts! Do you have any additional questions or comments? Would you like a copy of this interview once it is transcribed? Thank you again!

C. UK Interviews

1. At what stage of the approval process for inclusion in the NHS formulary has the HPV vaccine reached?

2. Are you aware of whether the Royal College of Obstetricians and Gynecologists (RCOG) and Royal College of Midwives (RCM) are taking a position on the HPV vaccine?

3. What would you say are the most important factors, pro and con, affecting the likelihood that NICE will approve the HPV vaccine for routine use in NHS patients? [Probe as needed with questions about the current political environment and explicit political pressure on NICE.]

4. Oftentimes, the U.S. Food and Drug Agency is closely watching drug and vaccine approval bodies in the UK and Europe, and the FDA is certainly very aware of NICE. Would you say that NICE paid any attention to FDA’s approval of Gardasil?

4. HPV vaccines are much more expensive than are Pap smears, and cost effectiveness is a much larger part of NICE’s mission than it is of the mission of the FDA. Could you give me
your perspective on the way a cost effectiveness case can – or can't – be made for HPV vaccines?

5. Would you expect any approval of an HPV vaccine for use in the NHS to include vaccination of boys as well as of girls? Why or why not?

6. And do you see any significant political conflict surrounding vaccination of pre-teens and young teenagers? That has caused controversy in the US because of fears that vaccination will promote promiscuity. Do you see such controversy arising here? Why or why not?

7. Last question! In your view, how serious ought we to be about whether Gardasil use might be associated with increased unplanned pregnancies, increased abortions, increased rates of other types of HPV, and increased rates of other STIs, including HIV? Would you say these are serious concerns, or not so serious? And what should the health system and the public health community do, starting now, to address any of these concerns?

Thank you so very much for your time and thoughts! Do you have any additional questions or comments? Would you like a copy of this interview once it is transcribed? Thank you again!
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