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Use of Media to Improve Human Papilloma Virus (HPV)Vaccine Acceptability

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USE OF MEDIA TO IMPROVE HUMAN PAPILLOMA VIRUS (HPV) VACCINE ACCEPTABILITY

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Our objective was to determine if using a video educational tool can influence (1) individual vaccine acceptability (2) parental acceptability, (3) parental views on vaccine mandates, and (4) age of vaccination accepted for the Human Papilloma Virus (HPV) vaccine. We conducted a cross-sectional study using bilingual surveys distributed at Brigham and Women's and Massachusetts General Hospital clinics and at the Coalition of Boston Public Health Association from January to March 2007. An initial 32-question survey addressing HPV knowledge, beliefs and vaccine acceptability was completed, followed by an eight-minute video about HPV and the vaccine. An additional 11-question post assessment was then completed. Five questions were extracted from both the pre/post questionnaires to evaluate HPV vaccine acceptability. Out of 256 subjects, 186 (73%) completed the video intervention and pre/post surveys. Of the 186, 66.6% (124) of subjects said they would vaccinate themselves. Individual acceptability increased after the video to 78% ($p=.0014$). An additional 55.8 % (102/186) of subjects supported making the HPV vaccine required for all children, with 51.1% (95/186) supporting vaccination if it were given at school and 66.7% (124/186) supporting child vaccination if it were free. After the video, this increased to 72.6% ($p<.0001$), 65.1% ($p<.0001$) and 86.6% ($p<.0001$) respectively. Initially, 56.5% (105/186) of subjects would vaccinate their child only if the child were older than 15 years of age; post-intervention, 82.3% of subjects accepted vaccination starting at age 9 and up ($p<.0001$). Secondary analysis revealed that Hispanic, Blacks and those with combined income less than $50,000 were more likely to not initially accept HPV vaccine for their children but showed high rates of acceptability after intervention. People's perception that vaccination will promote sex amongst the young was significant but did not affect overall acceptability. In conclusion, using multi-media as a way to increase knowledge significantly increased individual acceptability, parental acceptability, and age of acceptance of the HPV vaccine.

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I. Introduction

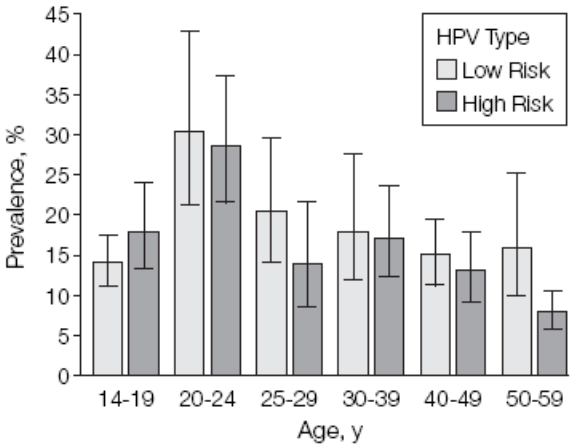
The approval of the quadrivalent Human Papilloma virus (HPV) vaccine (Gardasil© - HPV 6, 11, 16, 18) in June 2006 by the US Food and Drug Administration represented a landmark step in the prevention of cervical cancer. Persistent infection with certain subtypes of HPV has long been known to be associated with both cervical cancer and genital warts. A reduction in the acquisition of HPV could significantly lower the incidence of future high grade cervical lesions and reduce condylomatous disease. (1, 2) In order to achieve a reduction in population prevalence of HPV, full series vaccination of girls aged 11 to 26 is needed. Public health interventions that focus on understanding barriers and improving acceptability towards vaccination will be important in helping to achieve target levels of vaccination.

A. Incidence, Prevalence & Risk Factors

HPV is the most common sexually transmitted infection in the United States. Data from the National Health and Nutrition Examination Survey (NHANES) 2003-2004 suggests the prevalence of HPV infection to be as high as 26.8% (95% CI, 23.3%-30.9%) in a representative sample of 1,921 American women aged 14-59. (3) The NHANES group found a combined prevalence of the four vaccine types targeted by the quadrivalent vaccine (6, 11, 16 &18) of 3.4% and a combined prevalence of oncogenic subtypes 16 &18 of approximately 2%. Most notably, the study found that prevalence rose between the ages of 14-24 and then gradually declined until age 59, suggesting that younger women are at higher risk for acquiring HPV. [Figure 1]

Figure 1. From Dunne, et al (3)

Figure 1. Prevalence of Low-Risk and High-Risk HPV Types Among Females Aged 14 to 59 Years, NHANES 2003-2004



HPV indicates human papillomavirus; NHANES, National Health and Nutrition Examination Survey. Error bars indicate 95% confidence intervals. Both low-risk and high-risk HPV types were detected in some females. Low-risk HPV types are defined as HPV type 6, 11, 32, 40, 42, 44, 54, 55, 61, 62, 64, 71, 72, 74, 81, 83, 84, 87, 89, and 91; and high-risk HPV types as HPV type 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73, 82, 85, and IS39.

A second study, the National Longitudinal Study of Adolescent Health (ADHEALTH), looked specifically at US adolescents aged 18 to 25 and found a combined prevalence in this group of 26.9%. The ADHEALTH study identified a significantly lower prevalence in youth than the 49.3% prevalence of HPV infection in the 20 to 24 year old subgroup of the NHANES study. In their JAMA editorial, authors Weller and Stanberry (4)remark on this discrepancy (while noting the limitations in exact comparison between the two studies) and suggest that the method of viral detection – using urine samples in ADHEALTH vs. cervico-vaginal swabs in NHANES – could account for an underestimation of prevalence amongst younger women in ADHEALTH.

Independent risk factors for HPV acquisition in the NHANES study included age, marital status, and increasing number of lifetime and recent sexual partners. Of note, HPV prevalence in Black women was 39.2% versus 24.2% in non-Hispanic Whites and 24.3% in Mexican American women ($p<0.001$). (3) However, while race was a risk factor for HPV in bivariate analysis, this did not prove the case in the multivariate model. Further work on the NHANES data by Kahn et al (5) demonstrated that women living below the poverty line were more likely to be infected with a high-risk subtype of HPV than those living three or more times above it. One possible conclusion from this data is that socioeconomic status or other confounding factors and not race could account for the above differences in prevalence in Black women. In multivariate analyses of both studies, educational level was not associated either positively or negatively with HPV infection.

Given the natural history of HPV – exposure followed by viral clearance in the majority of women– it is logical to assume that a peak in infection would occur in women around the age of sexual debut and first exposure to the virus. It is also important to note that any study of prevalence will count a large number of infections that will clear on their own; only a small percentage of these persist, and it is these persistent infections that lead to pre-cancerous changes.

B. Establishing the connection between HPV and Cervical Cancer

Papillomaviruses have evolved to survive in the various transformation zones of the body and different subtypes have been linked to oropharyngeal, cervical, and anogenital cancers. The majority of cervical cancers arise in an area of the cervix called the transformation zone, so named because of the junction of stratified squamous epithelium of the ectocervix with the columnar epithelium of the endocervix. (6)

HPV types 16 and 18 are the subtypes most commonly linked to cervical cancer in the United States and the developed world. Together they are responsible for about 70% of cervical cancer and approximately 50% of cervical intraepithelial neoplasia (CIN) grade 3. Infection with two other subtypes of HPV, 6 and 11, accounts for 90% of genital warts. HPV subtype 16 is predominantly associated with the more common squamous cell cancers, while HPV type 18 has been strongly linked to adenocarcinomas arising from columnar glandular cells. Recent data suggests that cervical adenocarcinoma incidence has not decreased at the same rate as squamous cell carcinomas; this may in part be due to the fact that these cancers are located in the more internal columnar cells of the cervix and thus more often escape detection during PAP smears. Adenocarcinomas are also attributed with different risk factors and show different patterns of progression than squamous cell carcinomas.(7)

Transmission of HPV occurs through micro-tears in the mucosa, most commonly during sexual intercourse. Research suggests that the viral particles can travel from the vaginal introitus to reach cervical cells, suggesting that penetrative sexual intercourse is not necessary for transmission. Interestingly, some additional data suggests that male circumcision may reduce transmission of HPV; a proposed theory suggests keratinized penile epithelium may impede mucosal transfer. (6)

The HPV viral genome consists of only eight genes. Initial studies suggest that the mechanism of viral action for HPV involves two specific proteins, E6 and E7, which are encoded by the HPV genome (see Figure 2). E6 and E7 are onco-proteins with multiple cellular targets, most notably the p53 and retinoblastoma tumor suppression proteins (pRB) respectively. Inhibition of p53 by E6 leads to blockage of apoptosis, and inhibition

of pRB by E7 leads to cell cycle arrest. These proteins are expressed at low levels during infection. At a point during viral persistence deregulation occurs, leading to over-expression of the proteins in full thickness epithelium and subsequent changes in the cell cycle that lead to the development of pre-cancerous changes. (8)

Figure 2 Adapted from Schiffman, et al. (6)

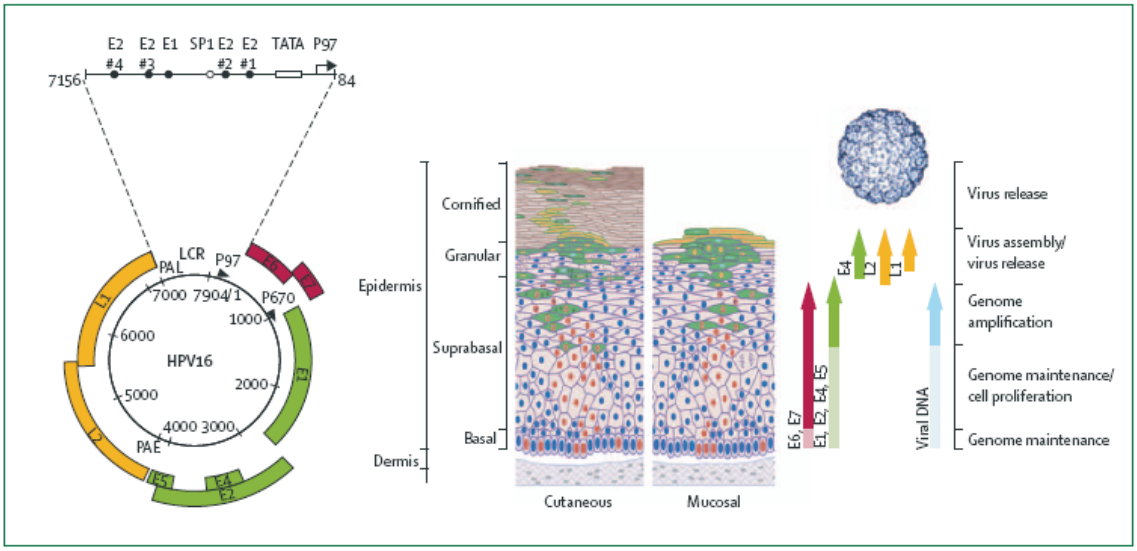


Figure 2: **The HPV genome and its expression within the epithelium**
The HPV genome consists of about 8000 bp of single-stranded, circular DNA. There are eight open reading frames and an upstream regulatory region. HPV genes are designated as E or L according to their expression in early or late differentiation stage of the epithelium: E1, E2, E5, E6, and E7 are expressed early in the differentiation, E4 is expressed throughout, and L1 and L2 are expressed during the final stages of differentiation. The viral genome is maintained at the basal layer of the epithelium, where HPV infection is established. Early proteins are expressed at low levels for genome maintenance (raising the possibility of a latent state) and cell proliferation. As the basal epithelial cells differentiate, the viral life cycle goes through success stages of genome amplification, virus assembly, and virus release, with a concomitant shift in expression patterns from early genes to late genes, including L1 and L2, which assemble into viral capsid. L1 is the major capsid protein while L2 serves as the link to the plasmid DNA. Adapted from Doorbar.[21]

C. Progression to Cancer

Approximately 30% of women newly infected with HPV show some abnormalities in cervical cytology. The majority of women will clear the infection within 2 years. However, in a subset of approximately 10% of these women, viral persistence occurs with a clone of infected cells that eventually progress to pre-cancer. Abnormalities detected on Pap that persist for greater than one year are therefore most concerning for pre-cancerous change. Of the HPV subtypes, HPV 16 is the most oncogenic, with a 40%

absolute risk of progression to pre-cancer if infected persistently for 3-5 years. Of note smoking, multiparity, and long term use of oral contraceptives (OCPs) can double to triple the rate of progression to pre-cancer. (6) Women with HIV also show increased viral persistence and longer time to clearance of HPV infections and may be at increased risk for progression to pre-cancer.

Abnormalities of the cervix are characterized by either cytological diagnosis (typically by a PAP smear) or a histological diagnosis. The cytological classification scheme includes the following designations: LSIL (Low Grade Squamous Intraepithelial Neoplasia), HSIL (High Grade Intraepithelial Neoplasia), ASC-US (Atypical Squamous Cells of Undetermined Significance) and ASC-H (Atypical Squamous Cells cannot exclude High Grade Lesion). The histopathological classification scheme includes the diagnoses of cervical intraepithelial neoplasia (CIN) Grades 1 through 3. It is important to realize that though a large number of pre-cancers are detected, not all of these will progress to invasive cancer. For further explanation of the significance, rates of progression, and management of lesions based on the above schemata, please refer to the following tables.

Table 1 Histological Classification and Management of Cervical Intra-epithelial Neoplasia[1,2]			
CIN 3 Severe Dysplasia or Dyskaryosis Carcinoma in Situ	Pre-Cancer	• 32-47% spontaneous regression • 12-36% to invasive cancer	**Excision or Ablation of T-zone** Then: • PAP or PAP+Colpo @4-6 mos (3 – then go to annual) • Or HPV @ 6mos (if – go to annual PAP) • If ASC, SIL, or HPV+ then repeat colposcopy
CIN 2	Equivocal – can be produced by non-carcinogenic HPV types. Data suggests 43-48% regress if untreated, 22% progress to CIN 3, 5% to invasive cancer	• 43-48% regression • 22% progression to CIN 3 • 5% progression to invasive CA	
CIN 1	Insensitive Histopathological sign of HPV Infection, one study suggests 51% regress.	• 47% regression • 21% progression to high grade • 0.15% to invasive CA	• **Serial pap at 6 & 12 mos** (2 – smears, return to annual, ASC or grtr →colpo) • Or **HPV test in 12 mos** with referral to colpo if + (if – go to annual Pap) • If post-menopausal or if fertility irrelevant, can go to excision.

Table 2 Cytological Classification and Management of Pre-Cancerous Changes [1,2]			
LSIL	Roughly corresponds to CIN 1, 15% risk of underlying CIN 2,3.	• 47% regress • 21% progress to high grade lesion • 0.15% to invasive cancer @ 24 mos	**Referral to Colposcopy +/- ECC** Post Menopausal Women & Adolescents: • Serial cytology in 6 & 12 mos • or HPV in 12 mos.
HSIL	Roughly corresponds to CIN 2,3 (70-75% risk)	• 35 % regress • 1.4% to invasive CA @24 mos	**Referral to Colposcopy +/- ECC** • If Colpo negative still recommend excision Adolescents • can have repeat

[1] Information compiled from Up to Date, American Society for Colposcopy & Cervical Pathology (ASCCP) Consensus Guidelines, and American College of Obstetricians and Gynecologists Guidelines. Progression rates from (38, 39). Note: Colpo = Colposcopy. PAP = Papanicolou test. ECC= Endo-Cervical Curretage

[2] Management may differ in HIV patients.

			colpo+ECC at 6 mos-1 yr
ASC – US **ASC – H**	Atypical Squamous Cells of Undetermined Significance Atypical Squamous Cells Cannot Exclude High Grade Lesion	• 68 % regression • 7 % progression to high grade lesion • 0.25% invasive CA @ 24 mos	

The average age of detection of those with viral persistence and precancerous changes is 10 years after sexual debut, which in the Untied States means peak detection of pre-cancerous changes at ages 25 to 35 years of age. The peak age range for detection of invasive cancers is subsequently age 35 to 55. It is important to note that the time between acquisition of HPV infection and the development of cancer can exceed 20 years.

HPV genetic testing is now available and is being utilized alongside PAP smears for detection and management of lesions. Screening with the HPV test can catch pre-cancerous changes often earlier than either cytology or colposcopy can, but also leads to the identification of a large number of changes related to recent infections which may clear on their own with time. Current American Cancer Society and American College of Obstetricians and Gynecologists (ACOG) recommendations suggest utilization of the HPV test as an adjunct to Pap screening in women over 30 (with a negative test leading to greater intervals between Pap testing) or in triage of women with equivocal ASC-US lesions on Pap smear.

There is still a great deal to be learned about the pathway of progression to cervical cancer. For example, research is unclear whether women do truly clear HPV

infections, or whether the virus can persist in a latent stage. The preponderance of HPV positivity in HIV patients may suggest that a latent stage is reactivated when the immune system is weakened. Studies must also substitute CIN II and II as surrogate markers for cervical cancer, since the standard of care requires treatment of lesions before they progress to cancer.

D. Epidemiology of Cervical Cancer

The American Cancer Society estimates that 11,150 cases of cervical cancer are diagnosed each year in the United States. Non-invasive cervical cancer (carcinoma in situ) is approximately 4 times more common than invasive cancer.(9) It is estimated that in 2007 about 3,670 women will die from cervical cancer. Death rates from cervical cancer have declined significantly in the last forty years as a result of increased use of the Papanicolou screening test and experts predict that they will continue to decline at a rate of approximately 4 % a year. Cervical cancer tends to disproportionately affect the worlds poorest regions; over 80% of cases occur in developing nations in Latin America, Sub-Saharan Africa, and India.(10)

Cervical cancer is clinically staged with the FIGO (International Federation of Gynecology and Obstetrics) System of Staging [Table 4]. This system classifies the disease in stages 0 through IV as determined by clinical spread of disease. Clinical spread is determined by a combination of physical examination, colposcopy, histopathology (on biopsy or conization), radiography (chest x-ray; CT, MRI, and PET to determine lymph node involvement), and endoscopy (cystoscopy or sigmoidoscopy). One randomized controlled trial evaluated surgical staging versus clinical staging and found no

difference(11); however, other evidence suggests improved results with surgical staging(12).

In the future FIGO recommendations may be modified to incorporate surgical staging; however, at present, especially given the preponderance of cervical cancer in developing countries without access to technology, the FIGO system remains clinically based. A rough guide to staging is as follows: Stage I (subdivided into IA1,IA2,IB1,IB2) corresponds to lesions confined to the cervix, Stage II (IIa,IIb) with spread to the vagina and then pelvis but not the lower 1/3 of the vagina or the pelvic side wall, Stage III (IIIa,IIIb) with spread into the lower third of the vagina or the pelvic wall, and Stage IV with spread to other organs.

The five year survival rate for the earliest stages (I-II) of invasive cervical cancer is 80-95% and 60% for Stage III.(10) The combined overall survival rate for all stages is 76%. (9) Treatment options typically involve some combination of surgery, chemotherapy, and radiation therapy [Table 3].

With this relatively high survival rate (in developed countries where access to surgery and radiation therapy is possible), the question arises as to the cost effectiveness and need for a mandatory vaccination. However, as discussed in the following sections, the vaccine may also have great cost-saving potential in terms of the millions of dollars spent on screening and treatment of abnormal cervical lesions in the United States.

Table 3 International Federation of Obstetrics and Gynecology (FIGO) Clinical Staging and Management of Cervical Cancer [3]

Stage	Description	General Management
IA1	Invasive carcinoma, confined to cervix, diagnosed only by microscopy. Stromal invasion ≤3 mm in depth and ≤7mmin horizontal spread	• **Hysterectomy** or **Conization** • Possible Radical Surgery or Radiation if Lymphovascular Involvement
IA2	Invasive carcinoma, confined to cervix, diagnosed only by microscopy. Stromal invasion >3 mm and ≤5 mm in depth and ≤7 mm in horizontal spread	• **Radical Hysterectomy** for ovarian preservation (+adjuvant chemo-radiotherapy if risk factors) or • **Radiotherapy** (outcomes similar) • **Radical Trachelectomy + Pelvic Lymphadenectomy** for preservation of fertility • Possible future for **Sentinel Node Biopsy** = Straight to radio-chemotherapy without radical surgery
IB1	Invasive carcinoma, confined to cervix, microscopic lesion >IA2 or clinically visible lesion ≤4 cm in greatest dimension	
IB2	Invasive carcinoma, confined to cervix, clinically visible lesion >4 cm in greatest dimension	
IIA	Tumor extension beyond cervix to vagina but not to lower third of vagina. No parametrial invasion	
IIB	Tumor extension beyond cervix. Parametrial invasion but not to pelvic side wall and not to lower Third of vagina	• **Chemo-Radiotherapy** (platinum based) then possible surgery
IIIA	Tumor extension to lower third of vagina but not to pelvic side wall	
IIIB	Tumor extension to pelvic side wall or causing hydronephrosis or non-functioning kidney	
IVA	Tumor invasion into bladder or rectum	
IVB	Distant metastasis	• Palliative **Chemotherapy**

[3] Adapted from (10)

E. Development of HPV Vaccines

There are currently two HPV Vaccines developed for primary vaccination, Gardasil (© Merck) and Cervarix (© GlaxoSmithKline). While both target the oncogenic HPV Subtypes 16 and 18, Gardasil also offers additional protection from HPV 6 and 11, subtypes which are common causes of genital warts. Both vaccines consist of virus-like-particles (VLPs), in this case the recombinant L1 protein of HPV expressed in yeast and self-assembled into non-infectious capsids. Intramuscular injection of the vaccine leads to production of high titers of neutralizing antibody, which are subsequently secreted into the vagina and cervix where they target HPV.

As of 2007 four major randomized, double-blind, placebo controlled studies have evaluated the efficacy of the HPV vaccines: one phase II study of the monovalent HPV 16 vaccine in 16-23 year olds (protocol 005), one phase II study of the quadrivalent vaccine in 16-23 year olds (protocol 007), and two phase III studies (protocols 013 and 015) of the quadrivalent vaccine in 16-23 and 16-26 year olds respectively. (13-15)The two phase II studies evaluated the efficacy of the vaccine on persistent infection with HPV, and the phase III studies took this one step further and looked at the effect on clinical lesions (CIN, Vaginal Intraepithelial Neoplasia (VIN), genital warts). Of note these clinical lesions must serve as surrogate endpoints for the effect of the vaccine on cervical cancer since current standards of care require pre-cancerous lesions to be treated before progression to cancer can be verified.

Table 4 CDC Recommendations of the Advisory Committee on Immunization Practice (ACIP): A Summary of Vaccine Efficacy Studies (16)

Outcome and protocol	Quadrivalent vaccine No.†	Quadrivalent vaccine Cases	Placebo No.	Placebo Cases	% Efficacy	(95% CI§)
HPV 16- or 18- related CIN 2/3 or AIS¶						
Protocol 005**	755	0	750	12	100.0	(65.1–100.0)
Protocol 007	231	0	230	1	100.0	(-3734.9–100.0)
Protocol 013	2,200	0	2,222	19	100.0	(78.5–100.0)
Protocol 015	5,301	0	5,258	21	100.0††	(80.9–100.0)
Combined protocols§§	8,487	0	8,460	53	100.0††	(92.9–100.0)
HPV 6-, 11-, 16-, 18- related CIN (CIN 1, CIN 2/3) or AIS						
Protocol 007	235	0	233	3	100.0	(-137.8–100.0)
Protocol 013	2,240	0	2,258	37	100.0††	(89.5–100.0)
Protocol 015	5,383	4	5,370	43	90.7	(74.4–97.6)
Combined protocols§§	7,858	4	7,861	83	95.2	(87.2–98.7)
HPV 6-, 11-, 16-, 18- related genital warts						
Protocol 007	235	0	233	3	100.0	(-139.5–100.0)
Protocol 013	2,261	0	2,279	29	100.0	(86.4–100.0)
Protocol 015	5,401	1	5,387	59	98.3	(90.2–100.0)
Combined protocols§§	**7,897**	**1**	**7,899**	**91**	**98.9**	**(93.7–100.0)**

Source: Adapted from Food and Drug Administration. Product approval information—licensing action, package insert: GARDASIL (quadrivalent human papillomavirus types 6, 11, 16, and 18), Merck & Co. Whitehouse Station, NJ: Food and Drug Administration; 2006. Available at http://www.fda.gov/cber/label/HPVmer060806LB.pdf.

* Populations consisted of persons who received all three vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, and were naïve (polymerase chain reaction–negative and seronegative) to the relevant HPV type(s) (types 6, 11, 16, and 18) before dose 1 and through 1 month post dose 3 (month 7). Median follow-up time for protocols 007, 013, and 015 was 1.9 years; median follow-up time for protocol 005 was 3.9 years.

† Number of persons with at least one follow-up visit after month 7.

§ Confidence interval.

¶ CIN: cervical intraepithelial neoplasis; AIS: adenocarcinoma in situ.

** Evaluated only the HPV 16 L1 VLP vaccine component of GARDASIL.

†† P-values were computed for pre-specified primary hypothesis tests. All p-values were <0.001, supporting the following conclusions: efficacy against HPV 16/18-related CIN 2/3 is >0 (protocol 015); efficacy against HPV 16/18-related CIN 2/3 is >25% (combined protocols); and efficacy against HPV 6/11/16/18-related CIN is >20% (protocol 013).

§§ Analyses of the combined trials were prospectively planned and included the use of similar study entry criteria.

Note: Point estimates and confidence intervals are adjusted for person-time of follow-up.

The vaccines were found to be highly effective. In fact, the combined efficacy of the trials against HPV 16 or 18 related CIN 2/3 or Adenocarcinoma in Situ (AIS) was 100% (CI 92.9-100.0). The efficacy against CIN 1 as well as the above was 95.2% (87.2-98.7), and the combined efficacy against subtype related genital warts was 98.9% (CI 93.7-100.0). (16)

The efficacy in the phase III trials was detected up to four years after initial vaccination; studies are ongoing to determine longer term efficacy. One phase II study showed a decline in antibody levels at 24 months followed by a plateau but maintained that antibody levels were still much higher than placebo or levels associated with previous infection. Another Phase II trial aims to follow Nordic women for at least 14 years with serologic testing for HPV at 5 and 10 years after vaccination. (16) Critics of compulsory vaccination point to the limitation of the time of follow up of current studies;

it is unclear as of now how long immunity persists and whether women may require a booster shot down the line.

In addition the data on the effect of vaccination on women already infected with one or more types of HPV is limited; initial data suggests that in women who are already HPV subtype DNA positive at baseline, the vaccine is significantly less effective (CIN preventive efficacies ranging from 39-47%). However, studies of antibody protection do show a boost after administration of the vaccine in women who already have natural immunity to a sub-type of HPV infection. (14)

F. Vaccination Guidelines

Gardasil is currently the only vaccine approved in the United States and has been approved for ages 9-26. Recommendations by the CDC Advisory Committee on Immunization Practice (ACIP) are for vaccination of girls 11 to 12 years of age, although the vaccine has been approved for ages 9 and above. (16)Catch up vaccination for girls aged 13 to 26 is recommended; however, the vaccine is most effective if given before sexual exposure and will have limited to no benefit in women who already have one or more of the subtypes of HPV found in the vaccine.

The vaccine is given in three doses at with the second and third doses administered 2 and 6 months after the first respectively. It has been approved for simultaneous administration with age-related Meningococcal vaccine and the Tdap booster. At this time immunogenicity and safety data is available on vaccination of men, but trials looking at efficacy are pending. The vaccine is not recommended for pregnant women, and has been classified as Category B in pregnancy based on animal studies.

G. Impacts of Vaccination

Estimates suggest that the prevention and treatment of anogenital warts and HPV related disease in the United States results in $4 billion or more in direct costs each year. Of this, approximately $200 million is attributable to genital warts, $300-400 million to invasive cervical cancer, and the rest to routine cervical cancer screening. (16)

Several models have been developed to evaluate both the public health and monetary impact of the HPV Vaccine in the United States. Goldie et al utilized a Markov model; a mathematical model that hypothetically follows 100,000 adolescent girls through their lifetime and estimates probabilities of transitioning between several health states (i.e. not infected, infected with one or more subtypes of HPV, exhibiting degrees of cytologic change on Pap smear, degrees of invasive cancer, etc) to determine endpoints such as quality-adjusted life years (QALY) gained and total cost. This type of modeling requires certain assumptions; in the case of Goldie et al, assumptions were made of 90% vaccine efficacy and achievement of full series vaccination in all girls at age 12. (17)

Goldie et al estimated an absolute lifetime risk of cervical cancer of 3.64% in the absence of any screening and a 0.86% risk with current screening practices. They were then able to show that full series vaccination of girls at 12 years of age against HPV subtypes 16 and 18 would lead to a decrease in the absolute lifetime risk of cervical cancer to 0.30-0.47%. The incremental cost-effectiveness of this vaccine (above current screening practices) would range from $20,600 (with 100% vaccine efficacy) to $33,700 (70% vaccine efficacy) per QALY. Other studies have used dynamic transmission models which incorporate the benefits of herd immunity, finding a 75% reduction in cervical cancer incidence at a much lower cost of $3,000 per QALY. (18). All cost effectiveness

assays are sensitive to variables such as duration of vaccine coverage, vaccine cost, and frequency of cervical cancer screening.

Further comparisons by Goldie et al of different combinations of prevention strategies (screening plus vaccination, screening alone, etc) were made, and the study determined the most effective strategy (with a cost effectiveness ration of less than $60,000 per QALY) to be vaccination at 12 years of age accompanied by triennial cytologic screening beginning at 25 years. This strategy would reduce the lifetime risk of cervical cancer by 94% compared to no screening; by comparison, vaccination with annual screening starting at age 18 years would cost more than $3.5 million per QALY.

The study reports that the proposed strategy of vaccination at 12 years with triennial pap screening is more effective than current screening practices and represents the best combination of cost and benefits. Most notably, it is a combination of prevention of costly high grade lesions and a lessening of the frequency of Pap smears required after vaccination that contributes to its cost-effectiveness in the US. This analysis of cost per QALY would obviously differ greatly in nations where screening practices are much less widespread and presentation of invasive cancers more common.

Even within the United States, a reduction in HPV acquisition would have a particularly strong impact on the low income and minority women who tend to be disproportionately affected by cervical cancer, improving their quality adjusted life expectancy years in a cost-effective manner. (19) According to data from the National Cancer Institute SEER Statistics from 2000-2004, the rate of cervical cancer is considerably high in Hispanic (13.8 per 100,000 women) and Black (11.4 per 100,000) women than in Caucasian women (8.5 per 100,000). Black and Hispanic women were

also more likely to die from cervical cancer than white women (mortality rates of 4.9 and 3.3 per 100,000 respectively). (20, 20) One explanation for racial disparities in incidence is differences in access to screening. A program that incorporates primary prevention through vaccination could therefore help to eliminate some of the racial disparities in cervical cancer in the United States. (16)

H. Current Knowledge of Vaccine Acceptability and Barriers to Vaccination

Despite the compelling data on the vaccine's efficacy and cost-effectiveness, formidable barriers to its universal adoption exist. A New England Healthcare Institute expert panel estimate suggests that the full series adoption rate amongst the initial target population will be only 15% in the first year.(19) Cited barriers to adoption include lack of knowledge about HPV, resistance to vaccinating minors, concern over school or government mandates for vaccination, and worries about vaccine safety.[5-9] (21)(21-25) An understanding of the role that education can play in influencing public acceptability towards vaccination is thus critical to ensure that the vaccine reaches its maximum public health potential.

To date the literature has yielded mixed results regarding the effects of education on public acceptability of vaccination. Lascano-Ponce et al showed that following being given information about HPV, a high percentage (83.6%) of Mexican women indicated they would allow their daughters participate in a trial of the HPV Vaccine; however, pre-education acceptance was not reported. (26)

Within the US, Dempsey et al randomized an educational sheet to half of 1600 parents of 8 to 12 year olds who were mailed a survey about HPV vaccination. Analysis of the 840 returned surveys found no significant differences in acceptability between

those given the educational sheet and the control group. (27) In comparison Davis et al did find a difference in acceptability post education. Parents were given an information sheet addressing prevalence of infection, mode of transmission, and severity of sequelae. After reading the materials, 37 % of parents of 10-15 year olds who were initially opposed to the vaccine changed their mind and 65% of undecided parents became in favor of vaccination.(28) Other qualitative studies have assessed general parental attitudes towards vaccination (especially towards vaccination for a sexually transmitted infection) and have found that in general parents are accepting of health recommendations that will protect their children, regardless of the mode of transmission of infection.(29, 30) Of note the majority of these studies were done prior to vaccine availability and the concurrent increase in media coverage both for and against the vaccine.

I. Vaccine Mandates and Public Opinion

Over 20 states in the US are currently considering laws to make HPV vaccination mandatory for pre-teen girls. The law governs that individual states and not the federal government have the authority to mandate vaccines. This has led to legislative debate on the individual state level involving both liberal and religious conservative groups. A storm of debate was initiated in Texas after the Republican Governor issued a mandate for vaccination of girls entering the 6th grade. The legality of this mandate is now being challenged by the state's attorney general on the basis that it infringes upon parental rights and may promote promiscuity. Legislation has already been defeated in Mississippi, West Virginia, Kentucky and New Mexico. (31-34) Though the New Mexico

legislation passed through the state House and Senates, it was ultimately vetoed by the state's Democratic governor

Prior reports addressing school mandates have been in the form of editorials and polls. The National Poll on Children's Health included in 48 states reported that 45% of parents support school mandates for HPV vaccination as compared to 68% parental support for a new teen vaccine that prevents tetanus, diphtheria and whooping cough (Tdap). (35) Opponents for HPV vaccination cite state legislation as an unwarranted intrusion on individual and parental rights. Proponents of mandating vaccination suggest that an "opt out" clause (by which parents can choose to opt out of mandated vaccination on religious or personal grounds) preserves parental autonomy while also promoting widespread achievement of public health goals.

Various groups have cited concerns that the vaccine would encourage sexual promiscuity amongst teens. Implicit in this is the idea that acknowledging teen sexuality is to promote it. Furthermore, teens are far more likely to react to the more immediate threats of AIDS or pregnancy in determining sexual action than to the remote risk of cervical cancer from HPV and the fact that they are protected from it.(32)

Opponents to mandating vaccination suggest abstinence as an easy and safe alternative. Data from the CDC shows that while only 13% of American girls are sexually experienced at 15, by 17 this number climbs to 43%, and by 19 years of age to 70%. Studies have also shown that abstinence only education does not necessarily delay or decrease the onset of sexual activity amongst teens.

Other arguments against vaccination cite the limited data on the longevity of protection offered by the vaccine and its unknown long term effects. It has been reported

that in many cases pediatricians have restricted themselves to educating and counseling objecting families, since the risks posed by going unvaccinated are not considered a danger to the health of communities given the mode of transmission. (32, 35)

II. Objective

It was our objective to determine whether use of a multimedia educational tool, given the current climate surrounding the HPV vaccine, could affect the following: 1) Individual vaccine acceptability 2) Parental vaccine acceptability and 3) Parental views on vaccine mandates, school vaccination, and acceptable age for vaccination. A secondary objective included identifying whether acceptance post education varied amongst ethnic, socioeconomic, and religious/cultural subgroups.

III. Methods

Surveys for this cross-sectional, voluntary study were distributed to 256 women between the ages of 18 and 60 during a period extending from January to March 2007. Institutional approval was obtained from the Partners Institutional Review Board committee. Subjects were recruited from the following sites: Brigham and Women's Obstetrics and General Gynecology Clinics, Pap Smear Evaluation Clinics at both Brigham and Women's and Massachusetts General Hospitals, and the REACH 2010 Coalition of the Boston Public Health Association.

Those recruited from clinic sites were approached while in the waiting area by a bilingual research team member and asked to participate. All study materials were available in both English and Spanish. Subjects who agreed to participate (258) completed a 32-question initial assessment addressing general knowledge and beliefs about HPV as well as a section on demographic information and sections addressing both

parental and individual vaccine acceptability. These subjects were then asked to watch an eight-minute video about HPV and the vaccine. The educational video used was produced by the research team and consists of 3 segments addressing: 1) facts about HPV and transmission 2) prevalence and incidence of HPV and 3) information about the vaccine. [Table 5]. Those that watched the video (186 subjects) then completed an additional 11-question post-survey assessment.

Table 5 Educational Video Content

Section I

What is HPV?
How is HPV transmitted?
How does HPV lead to cervical cancer & genital warts?
What can you do about HPV?

Section II

How common is HPV?
How and when are youth affected by HPV?
What are risk factors for acquiring HPV?

Section III

What is a vaccine?
What does the HPV vaccine protect against?
What are the side effects of the vaccine?
How is it given?
Who can get it?

Five questions were extracted from pre and post questionnaires to evaluate HPV vaccine acceptability. These questions would address whether participants would 1)self-vaccinate 2) vaccinate their children 3)support making the vaccine mandatory for all children 4)vaccinate their children if the vaccine were free and lastly subjects were asked to identify 5)the youngest age at which they would vaccinate their children. Primary statistical analysis of the data was performed using the McNemar test to evaluate the effectiveness of the video intervention. Secondary analyses were performed using the Chi

squared and Fisher's Exact tests to determine whether specific factors played a role in acceptability.

IV. Results

Of the 256 subjects that participated in the study, 73% (n=186) completed the video intervention and surveys. Eighty percent (n=150) of the subjects had heard of HPV, while 65% (n=120) of subjects knew the HPV vaccine was available prior to viewing the video. The demographics of the study population are listed in Table 1. The majority of study participants identified as Black or Hispanic (55%), with 27 % self-identifying as Caucasian.

Participants were primarily single (43%), working individuals (57%) who had some college education (40%). Sixty percent admitted to being part of a Christian religious sect. Sixty-six percent of our participants had an overall combined annual income that was less than $50,000.

Table 6 Demographic Information (n=178)

Demographic Characteristics	n (%)
Median Age, years (mean,standard deviation)	30 (33, 11)
Income ($)	
10,000 – 20,000	66 (39.3)
20,000 – 50,000	55 (32.7)
50,000 and greater	47 (26.4)
Race	
Hispanic	66 (40)
Black	28 (17)
Caucasian	10 (6)
Other	61 (34)
Education	
Grades 1-12	23 (13)
High School Graduate	32 (18)
Some College	57 (32)
College Graduate	39 (22)
Graduate School	26 (14.6)
Religion	
Roman Catholic	65 (39)
Protestant (Christian)	43 (25)
Jewish	5 (2.8)
Other	33 (18.5)
Not Religious	23 (12.9)
Marital Status	
Not Married	78 (45)
Living with partner	34 (20)
Married or Partnered	51 (29)
Divorced or Separated	9 (5)
Widowed	2 (1)
Work	
Currently Working	100 (58)
In School	25 (15)
Homemaker	14 (8)
Unemployed	19 (11)
Retired	4 (2)
Disabled	9 (5)
Children	
Have Children, mean number of kids	96 (57), 2
No Children	74 (43)

Prior to the intervention 67% (n=124) of subjects were willing to receive the vaccine for themselves, and 67% (n=124) indicated they would vaccinate their child if the vaccine were free [Table 7],. Fifty-five % (n=102) agreed that the vaccine should be required for all children, while 51% (n=95) would agree to vaccination at school.

After watching the video, individual acceptability increased to 78% (p=.0014) and parental acceptability of free vaccination for children increased to 87 percent (p<.0001). Support for making the vaccine mandatory and administering it in school also increased to 73% (p<.0001) and 65% (p<.0001) respectively. [Figure 2]

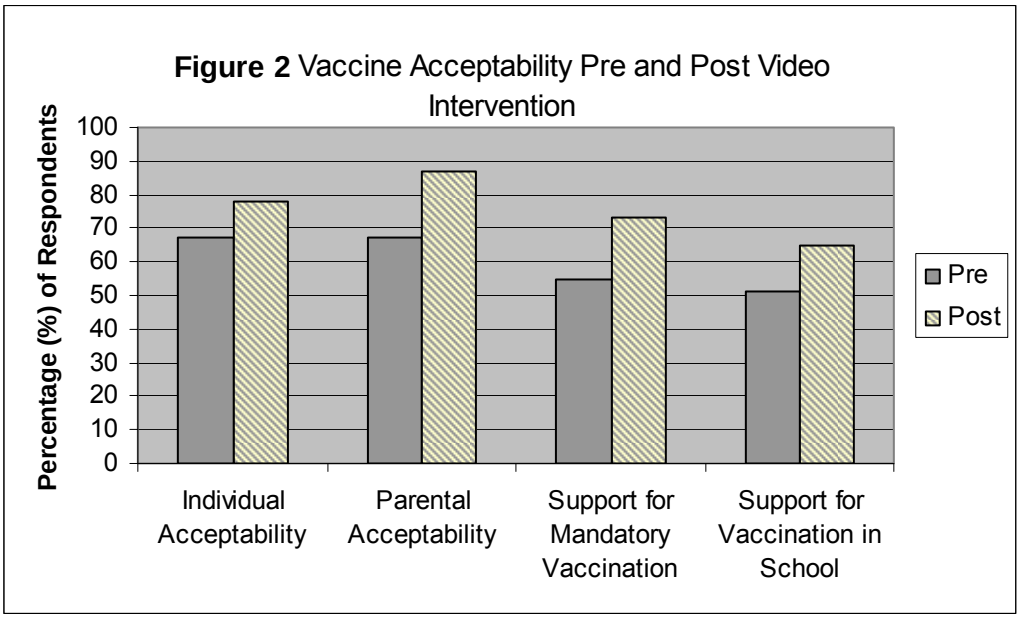
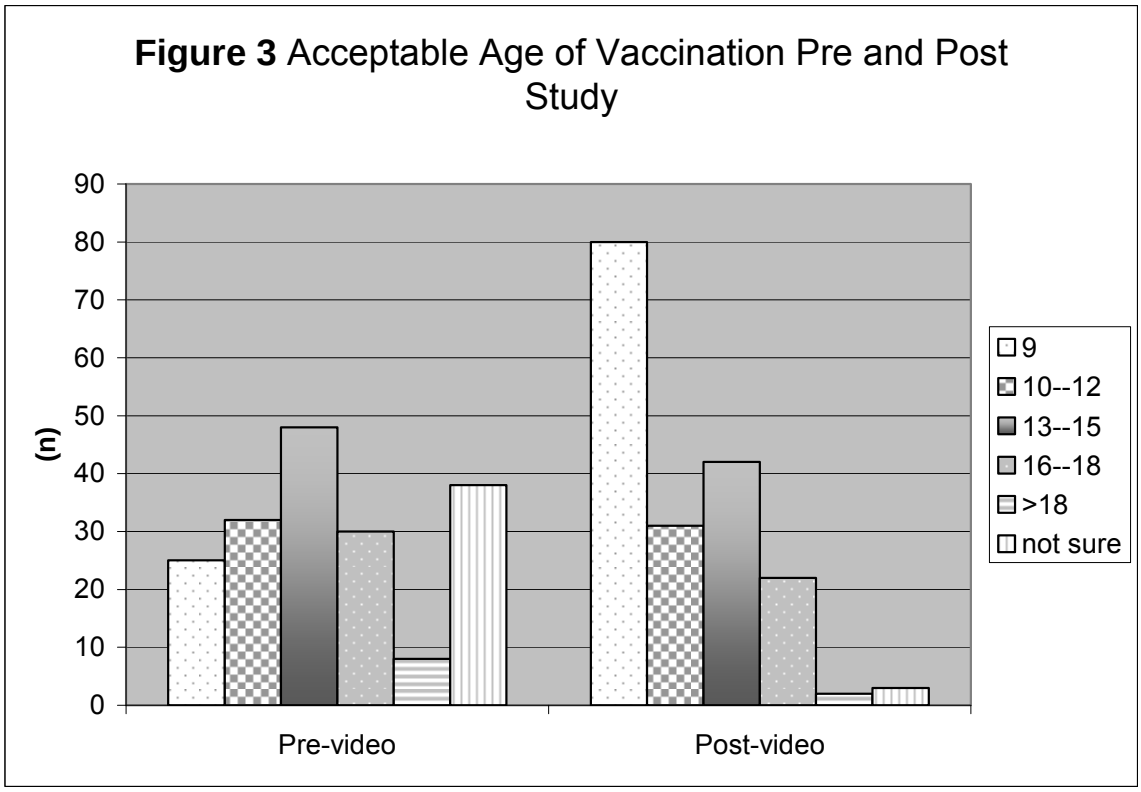


Table 7 Vaccine Acceptability Pre and Post Video Intervention

	Pre-Intervention (n=186)	Post-Intervention (n=186)	*P*-value
Would you vaccinate yourself?	67% (124)	78% (145)	0.0014
Would you make the vaccine required for all children?	55% (102)	72% (135)	<0.0001
Would you vaccinate your child if it were given at school?	51% (95)	65% (121)	<0.0001
Would you vaccinate your child if it were free?	67% (124)	86% (161)	<0.0001

Prior to intervention, the acceptable age of vaccination was 16 years or older in 56 % of subjects. After the intervention, 82.3 % ($p<.0001$) of subjects were willing to accept vaccination of children starting from age 9 and up. [Fig 3]



Secondary analysis revealed that Hispanic, Blacks and those with combined income less than $ 50,000 were the subgroups that were more likely to initially decline the vaccine but after the intervention were the groups most likely to accept vaccination for their children. [Figures 8 & 9] Of the subgroups who did not accept the vaccine and those who changed their minds after the video, the perception that the vaccine would promote sex did not seem to play a role in acceptability. In fact the majority of participants (62%) did not believe the vaccine would promote sexual activity in young people (n=114/183). Sixty-one percent (n= 113/186) of participants had children, and of these parents 44 % (n=50/113) said they talked to their children about sex. Whether the

participants talked to their children about sex and whether they had children did not affect acceptability.

Table 8 Change in Acceptability by Ethnic Group							
		Caucasian	**Hispanic**	**Black**	Other/No response	Total	Fisher's Exact Test
Would you vaccinate your child if the vaccine were free?	Group 1*	7	**1**	**7**	3	18	0.0287
	Group 2*	6	**13**	**22**	3	44	

Table 9 Change in Acceptability by Income Level							
		0-20K	**21K-50K**	51K+	No response	Total	Fisher's Exact Test
Would you vaccinate your child if the vaccine were free?	Group 1*	**4**	**6**	7	1	18	0.0723
	Group 2*	**20**	**17**	5	2	44	

* Group 1 = would not give vaccine even after video. Group 2 = initially said no but changed to yes post video.

Eighty-three percent (n=154/186) of participants were able to name at least one of the following correct answers when asked what HPV causes: genital warts, precancerous changes (cervical dysplasia), abnormal pap smears, cervical cancer, or cancer of the vagina. There was no significant difference between Hispanics, Blacks, and Caucasians in their ability to answer this question correctly.

Amongst the questions answered by all participants (n=256) and not just those completing the video, we found that the majority of participants (64%, 165/256) thought the vaccine should be available for both men and women. Participants identified the following as very important in their decision to get a vaccine: safety (n=234/256, 91%),

side effects (214/256, 84%), and how long it would last (178/236, 70%). Ease of access, number of doses, and cost followed in importance. When asked where they would go for more information about the vaccine, 85% (n=218/256) said they would go to their doctor, while 70% (n=178/256) cited the internet.

V. Discussion

In order to maximize the impact of the Human Papillomavirus Vaccine, policy-makers will need a broad understanding of both current public acceptance and potential barriers to vaccination. Our study found high initial individual and parental (66 and 68 % respectively) acceptance of vaccination amongst a diverse urban sample of women aged 16 to 80.

These numbers correspond generally to high rates of acceptability found by previous studies. Most recently (but still prior to vaccine availability), Slomovitz et al found individual and parental acceptance rates of 77% and 67% in a population of urban Texan women.(36) A prior study by Davis of 575 parents of 10 to 15 year olds found a pre-education acceptance rate of 55 percent, and an earlier study in 2003 by Kahn et al of 52 female parents found even higher individual and parental acceptance (85% and 83% respectively).(28, 37) These relatively high rates of vaccine acceptability help to mitigate claims that the public acceptance serves as a significant barrier to vaccine delivery. Moreover, our study suggests that public opinion can be influenced by directed education from media sources. Use of a multi-media instrument in the form of an educational video significantly increased overall individual and parental acceptability to 78 and 87%, respectively. It is possible that the mixed results obtained by previous studies (26-28, 37) on the effect of education could reflect the mode of education used; multimedia methods

may influence acceptability more than written materials. We find it particularly encouraging that after viewing our video, parents were significantly more willing to vaccinate children at younger ages (age 9 and above versus age 16). Given that the vaccine is maximally effective when administered prior to the onset of sexual activity, vaccinating children at a younger age would improve target efficacy.

Our study suggests that public opinion of a vaccine mandate could also be influenced by education. Although only 55% of our population initially supported mandatory vaccination with only 51% approval of vaccination in school, following viewing our video vaccination approval rates rose to 72% and 65% respectively. Although this is true, the lowest rate of acceptability was found with in school vaccination, which may indicate that this is something the public may not be ready for.

As for the concern that the vaccine could promote sexual activity, a great deal of research supports the claim that sex education and condom distribution do not lead to an increase in sexual activity. Studies have shown that comprehensive sex education actually reduces the frequency of sex, delays initiation of sexual intercourse and reduces the number of sexual partners. [18-20]. Over half (62%) of all participants in this study did not believe the HPV vaccine would lead to increased sexual activity among recipients. In light of the fact that a great deal of media attention has been devoted to claims that the vaccine could encourage sexual activity in teens, the fact that the majority of our study population did not feel this to be the case is encouraging.

The question of cost still seems to be an important one within the HPV vaccination debate. Who will pay for the mandated vaccine? Policy makers have not answered the question if consumers, insurers, federal agencies, or states will bear the

cost. Our study revealed that the greatest change and increase in acceptance for vaccination for children in the context of free vaccination. Though individuals did not rank cost very highly amongst factors that would influence their willingness to receive a vaccine (safety, side effects, and duration of protection were most important), it no doubt plays a role. Finding a way to address cost issues will be important to help ensure broad spectrum access.

Aggressive marketing campaigns by Merck for Gardasil nationwide have no doubt played a role in increasing public knowledge and awareness of the need for HPV vaccination. The positive ramifications of this are evident in our study, as 81 percent of the study population was able to name correctly at least one sequelae of HPV infection. A review of media representation of HPV by Calloway et al found that ads were not always specific in clearly explaining the connections between HPV and Cervical Cancer. [15] It is for this reason that we advocate the development of other media tools to educate about HPV and ensure that women understand the links between HPV, abnormal Pap smears, genital warts, and cervical cancer.

Our educational intervention also demonstrated that lower income, minority populations may be the best target population to affect change in attitudes towards the HPV vaccine using this educational tool. Our experience revealed that utilization of video as a way to educate helped keep the individual focused and interested in the material and addressed misunderstandings of information presented by use of visual aids. This may be more effective in subgroups where public-based health clinics service lower income or less educated populations.

Our data showed that a novel approach of educational intervention by video improved rates of parental vaccine acceptability, in a minority, predominantly underserved population. Nevertheless, this study may have been influenced by several factors, including selection bias whereby the majority of participants were solicited from a gynecology and gyn-specific colposcopy clinic. These subjects may have been sensitized to the impact of HPV and the possible influence of the HPV vaccine, more than a population solicited in a different community setting. Although the participation rate was relatively high at 73%, they may also have been more inclined to participate within the setting of a gynecology clinic than at a local community site. These results may not be directly applicable to the general population.

Furthermore, since all subjects were female, the knowledge and acceptance rate of males of this same topic remains unknown. We cannot speculate on whether fathers would be as knowledgeable or inclined to support vaccination of their daughters. Additionally, we have not tested whether other intervention methods such as books, pamphlets, posters, or acoustic means such as through radio-ads would be as affective. Although our video did show a significant increase in parental vaccine acceptability after viewing, this intervention method may not be entirely practical or feasible in all settings. We also do not know if large scale application of our video intervention would produce the same effect as that viewed intimately on a laptop or within a small group setting as was done in this study.

In order to determine the full utility of a video intervention to increase acceptability of the HPV vaccine, a larger study targeted to both women and men of a variety of ages, of racial and social backgrounds, and from a variety of community

settings may help us answer the questions posed above. In this manner, we may better identify and target the populations most vulnerable to developing cervical dysplasia and cancer.

The HPV vaccine represents a rare public health opportunity to protect a large cohort of individuals from a devastating illness, not to mention the psychological and economic tolls of screening practices. Achieving target levels of vaccination will require sophisticated programs to counter barriers such as cost, access, and individual acceptance. Our study suggests that education, in this case through multimedia, can have a powerful effect on the latter. Thus, by utilizing this information to develop appropriate educational tools, we can directly impact rates of cervical dysplasia, genital warts, and cervical cancer in the near and distant future.

Appendix I. Sample Survey

1. Please Circle: MALE FEMALE	
2. I have heard of a virus called Human Papillomavirus (HPV).	Please circle: Yes No *Not Sure*
3. Can you be tested for Human Papilloma Virus (HPV)?	☐ Yes ☐ No ☐ I don't know

4. What does HPV cause? (Circle all that you think apply)

Genital Warts	Infertility *(cannot have children)*
Herpes	Premature Birth
Precancerous Changes (Cervical Dysplasia)	Abnormal PAP smears
Cervical Cancer	AIDS
I Don't Know	Cancer of the Vagina

5. Do you know what a Pap smear tests for?	☐ Yes ☐ No ☐ Not Sure
6. ONLY ANSWER IF YOU SAID YES TO QUESTION 4: what does a Pap smear check for? Mark all that might apply.	☐ Chlamydia or Gonorrhea ☐ Pre-Cancerous Cells ☐ Cervical Cancer ☐ Fertility ☐ Yeast Infections

7. How is HPV spread from one person to another? (Circle all that you think apply)	
Kissing Close skin contact without sexual intercourse Oral Sex I Don't Know	Anal Sex Sexual Intercourse Sitting on public toilets From someone's cough

8. Condoms prevent spread of HPV.	☐ Always ☐ Sometimes ☐ Never ☐ I don't know
9. Taking the birth control pill prevents you from getting infected with HPV.	☐ Yes ☐ No ☐ I don't know
10. Have you ever had a sexually transmitted disease?	☐ Yes ☐ No ☐ Not Sure
11. FOR WOMEN ONLY: Have you ever been told you had an abnormal Pap smear and/or precancerous change?	☐ Yes ☐ No ☐ I don't know
12. FOR WOMEN ONLY: Have you had cervical cancer?	☐ Yes ☐ No
13. Have you or any of your family members had cancer?	☐ Yes ☐ No ☐ I don't know.
14. Have you talked to your child about sex?	☐ Yes ☐ No ☐ Don't have kids

15. Who talks to your children about sex? (mark all that apply)		
☐ Myself ☐ Child's School ☐ Church group or religious leader	☐ Other youth activity programs ☐ Media (TV or radio or internet)	☐ Child's Doctor ☐ My kids are too young to talk about sex ☐ Other: _____
16. If you have not talked to your children about sex, why not?		
☐ My child is too young. ☐ Someone else has talked to them already. ☐ My child's school will talk to them.	☐ I am not comfortable talking to them about sex. ☐ I have no time to talk to them about sex.	☐ My child will not listen to me ☐ Other: _____

17. I knew before today that there is an HPV vaccine.	☐ Yes ☐ No ☐ I'm not sure
18. Who do you think the vaccine should be for?	☐ Women only ☐ Men only ☐ Women and Men ☐ Should not be available.
19. What is the youngest age you would give your child the vaccine?	☐ 9 ☐ 10-12 ☐ 13-15 ☐ 16-18 ☐ Older than 18 ☐ Not Sure ☐ I would not give my child the vaccine.
20. Would you vaccinate your child if the vaccine is free?	☐ Yes ☐ No ☐ I'm not sure

21. Would you vaccinate your child if the vaccine were given at school?	☐ Yes ☐ No ☐ I'm not sure
22. If your doctor recommends the HPV vaccine would you give it to your child?	☐ Yes ☐ No ☐ I'm not sure
23. Would you support making the HPV vaccine required for all children?	☐ Yes ☐ No ☐ I'm not sure
24. Do you think giving young people the HPV vaccine will make them more likely to have sex?	☐ Yes ☐ No ☐ I'm not sure

25. How would you describe the HPV vaccine to your child? Mark all that apply.

☐ It prevents cervical cancer. ☐ It prevents a sexually transmitted disease.	☐ All girls get the vaccine. ☐ It prevents women's diseases,	☐ Not sure ☐ Other: _____

26. If you answered "not sure" to questions 17-23, is it because you don't know enough about the HPV vaccine?

☐ Yes ☐ No ☐ Other reason (please explain: _____

_____

_____

27. (FOR MEN AND WOMEN BOTH) Would you get the vaccine yourself?	☐ Yes ☐ No ☐ I am not sure
28. Would you get the vaccine to protect your partner(s)?	☐ Yes ☐ No ☐ I am not sure
29. If your doctor recommends the HPV vaccine would get it?	☐ Yes ☐ No ☐ I am not sure

30. Would your partner (husband, wife, boyfriend or girlfriend) support your decision to get the HPV vaccine?	☐ Yes ☐ No ☐ I am not sure

31. How important are the following items when you think about getting a vaccine?

	Very Important	Neutral	Not Important
Safety	☐	☐	☐
How Easy it Would be to Get It	☐	☐	☐
Side Effects	☐	☐	☐
Number of Doses I Would Need	☐	☐	☐
Cost	☐	☐	☐
How Long it Lasts	☐	☐	☐

32. Where would you go to find out more about the HPV vaccine? (Mark all that apply)

☐ Radio	☐ Friend	☐ Church group
☐ Internet	☐ Community Group	☐ Doctor
☐ Television	☐ Other people of the same race only.	☐ Child's doctor (pediatrician)
☐ Library	☐ School Staff	☐ Other family members
	☐ Other extended family members	☐ I would not look for any more information.

☐ Other: _____

After learning more about HPV, please answer questions below:

1. Who do you think the vaccine should be for?	☐ Girls only ☐ Boys only ☐ Boys and Girls ☐ Should not be available.

2. What is the youngest age you would give your child the vaccine?	☐ 9 ☐ 10-12 ☐ 13-15 ☐ 16-18 ☐ Older than 18 ☐ Not Sure ☐ *I would not give my child the vaccine.*
3. Would you vaccinate your child if the vaccine is free?	☐ Yes ☐ No ☐ I'm not sure
4. Would you vaccinate your child if the vaccine is given at school?	☐ Yes ☐ No ☐ I'm not sure
5. Would you support making the vaccine required for all children?	☐ Yes ☐ No ☐ I'm not sure
6. If your doctor recommends the HPV vaccine would you give it to your child?	☐ Yes ☐ No ☐ I'm not sure
7. Do you think giving young people the HPV vaccine will make them more likely to have sex?	☐ Yes ☐ No ☐ I'm not sure

8. How would you describe the HPV vaccine to your child? Mark all that apply.

☐ It prevents cervical cancer. ☐ It prevents a sexually transmitted disease.	☐ All girls get the vaccine. ☐ It prevents women's diseases,	☐ Not sure ☐ Other: _____

9. Would you get the vaccine yourself?	☐ Yes ☐ No ☐ I am not sure
10. Would you get the vaccine to protect your partner(s)?	☐ Yes ☐ No ☐ I am not sure

11. How important are the following items when you think about getting a vaccine?

	Very Important	Neutral	Not Important
Safety	☐	☐	☐
How Easy it Would be to Get It	☐	☐	☐
Side Effects	☐	☐	☐
Number of Doses I Would Need	☐	☐	☐
Cost	☐	☐	☐
How Long it Lasts	☐	☐	☐

Demographics (Information for survey purposes only)

1. What is your age? _____

2. Please circle: Female Male

3. What is your marital status?

- ☐ Not married
- ☐ Living with partner but not married
- ☐ Currently married or partnered
- ☐ Divorced or legally separated
- ☐ Widowed

4. What is your ethnic background?

- ☐ Latina or Hispanic:
  - ☐ Cuban
  - ☐ Dominican
  - ☐ Puerto Rican
  - ☐ Central American
  - ☐ South American
  - ☐ Mexican
  - ☐ Other: _____
- ☐ African American
- ☐ Native American
- ☐ Native Hawaiian
- ☐ Other Ethnic Group:

_____

- ☐ Caribbean/West Indian:
  - ☐ Haitian
  - ☐ Jamaican
  - ☐ Trinidadian
  - ☐ Other:

_____

- ☐ Asian:
  - ☐ Vietnamese
  - ☐ Cambodian
  - ☐ Laotian
  - ☐ Chinese
  - ☐ Japanese
  - ☐ Indian
  - ☐ Other:

_____

- ☐ European:
  - ☐ Irish
  - ☐ Italian
  - ☐ Russian
  - ☐ Other:

_____

- ☐ Jewish
- ☐ Middle Eastern
- ☐ African:
  - ☐ Somalian
  - ☐ Nigerian
  - ☐ Senegalese
  - ☐ Cape Verdean
  - ☐ Other:

_____

5. What is your zip code?	
6. What is your highest level of education?	☐ No formal school ☐ Grades 1-12 (primary) ☐ High school graduate (secondary) ☐ Some college ☐ College graduate ☐ Graduate School ☐ Vocational/ Tech school
7. Which of the following best describes your work?	☐ Currently Working ☐ In School (Student) ☐ Homemaker (housewife) ☐ Unemployed (not working) ☐ Retired ☐ Extended Sick Leave ☐ Disabled ☐ Other: _____

8. If you are currently working, what do you do?

☐ Retail Store Clerk	☐ Management	☐ Community & Social Services
☐ Healthcare Support (Home Health Aid, Nurse's Aid, Medical Assistant)	☐ Business and Financial	☐ Education, Training & Library
☐ Protective Services (Firefighter, Police Officer)	☐ Computer and Mathematical	☐ Arts, Design, *Media, Sports & Entertainment*
☐ Food Preparation & Serving (cook, fast food restaurant work).	☐ Architecture and *Engineering*	☐ Healthcare Practitioners and Technical Work
☐ Building, Grounds Cleaning, & Maintenance	☐ Life, Physical, & Social Science	☐ Other
	☐ Legal Occupations	

8. What is your total annual household income?	☐ Less than $10,000 ☐ $10,000 to $20,000 ☐ $21,000 to $30,000 ☐ $31,000 to $50,000 ☐ $51,000 to $100,000 ☐ Over $100,000
9. (WOMEN ONLY) Where do you get your Pap test?	☐ I don't know what a Pap test is. ☐ Primary Care Doctor ☐ Ob-Gyn ☐ I don't get Pap tests. ☐ Pediatrician ☐ Other_____
10. What type of heath insurance do you currently have?	☐ Medicare ☐ Medicaid or Mass Health? ☐ Private Insurance through my work or my spouse's work. ☐ Get free care. ☐ I do not have health insurance.
11. What is your religion?	☐ Roman Catholic ☐ Jewish ☐ Protestant (Christian) ☐ Muslim ☐ Not Religious ☐ Other: _____
12. How much does your faith, religion affect your decisions about health?	☐ Not at all ☐ Somewhat (a little) ☐ Most of the time ☐ Affects all my health decisions
13. Do you have children? ☐ Yes ☐ No If yes, please answer questions 14 and 15.	14. How many children do you have? _____

15. Please list your children by age and if they are a girl or boy.

Age	Boy	Girl
1.	☐	☐
2.	☐	☐
3.	☐	☐
4.	☐	☐
5.	☐	☐
6.	☐	☐
7.	☐	☐
8.	☐	☐

15. I give my children all the vaccines recommended by their doctor.	☐ Yes ☐ No ☐ Sometimes

VI. References

1. Dasbach, E.J., Elbasha, E.H., and Insinga, R.P. 2006. Mathematical models for predicting the epidemiologic and economic impact of vaccination against human papillomavirus infection and disease. *Epidemiol Rev 28:88-100* **28**:88-100.

2. Lehtinen, M., Apter, D., Dubin, G., Kosunen, E., Isaksson, R., Korpivaara, E.L., Kyha-Osterlund, L., Lunnas, T., Luostarinen, T., Niemi, L. et al. 2006. Enrollment of 22,000 adolescent women to cancer registry follow-up for long-term human papillomavirus vaccine efficacy: guarding against guessing. *Int J STD AIDS 17(8):517-21* **17**:517-21.

3. Dunne, E.F., Unger, E.R., Sternberg, M., McQuillan, G., Swan, D.C., Patel, S.S., and Markowitz, L.E. 2007. Prevalence of HPV infection among females in the United States.[see comment]. *Jama 297(8):813-9* **297**:813-9.

4. Weller, S.C., and Stanberry, L.R. 2007. Estimating the population prevalence of HPV.[comment]. *Jama 297(8):876-8* **297**:876-8.

5. Kahn, J.A., Lan, D., and Kahn, R.S. 2007. Sociodemographic factors associated with high-risk human papillomavirus infection. *Obstet. Gynecol.* **110**:87-95.

6. Schiffman, M., Castle, P.E., Jeronimo, J., Rodriguez, A.C., and Wacholder, S. 2007. Human papillomavirus and cervical cancer. *Lancet* **370**:890-907.

7. Sherman, M.E., Wang, S.S., Carreon, J., and Devesa, S.S. 2005. Mortality trends for cervical squamous and adenocarcinoma in the United States. Relation to incidence and survival. *Cancer* **103**:1258-1264.

8. Mantovani, F., and Banks, L. 2001. The human papillomavirus E6 protein and its contribution to malignant progression. *Oncogene* **20**:7874-7887.

9. Anonymous ACS :: Detailed Guide: Cervical Cancer. **2008**.

10. Petignat, P., and Roy, M. 2007. Diagnosis and management of cervical cancer. *BMJ* **335**:765-768.

11. Lai, C.H., Huang, K.G., Hong, J.H., Lee, C.L., Chou, H.H., Chang, T.C., Hsueh, S., Huang, H.J., Ng, K.K., and Tsai, C.S. 2003. Randomized trial of surgical staging

(extraperitoneal or laparoscopic) versus clinical staging in locally advanced cervical cancer. *Gynecol. Oncol.* **89**:160-167.

12. Lagasse, L.D., Creasman, W.T., Shingleton, H.M., Ford, J.H., and Blessing, J.A. 1980. Results and complications of operative staging in cervical cancer: experience of the Gynecologic Oncology Group. *Gynecol.Oncol.* **9**:90-98.

13. Mao, C., Koutsky, L.A., Ault, K.A., Wheeler, C.M., Brown, D.R., Wiley, D.J., Alvarez, F.B., Bautista, O.M., Jansen, K.U., and Barr, E. 2006. Efficacy of human papillomavirus-16 vaccine to prevent cervical intraepithelial neoplasia: a randomized controlled trial. *Obstet. Gynecol.* **107**:18-27.

14. Villa, L.L., Ault, K.A., Giuliano, A.R., Costa, R.L., Petta, C.A., Andrade, R.P., Brown, D.R., Ferenczy, A., Harper, D.M., Koutsky, L.A. et al. 2006. Immunologic responses following administration of a vaccine targeting human papillomavirus Types 6, 11, 16, and 18. *Vaccine* **24**:5571-5583.

15. Villa, L.L., Costa, R.L., Petta, C.A., Andrade, R.P., Ault, K.A., Giuliano, A.R., Wheeler, C.M., Koutsky, L.A., Malm, C., Lehtinen, M. et al. 2005. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. *Lancet Oncol.* **6**:271-278.

16. Markowitz LE. Dunne EF. Saraiya M. Lawson HW. Chesson H. Unger ER. Centers for Disease Control and Prevention (CDC). Advisory Committee on Immunization Practices (ACIP). 2007. Quadrivalent Human Papillomavirus Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* **56**:1-24.

17. Goldie, S.J., Kohli, M., Grima, D., Weinstein, M.C., Wright, T.C., Bosch, F.X., and Franco, E. 2004. Projected clinical benefits and cost-effectiveness of a human papillomavirus 16/18 vaccine. *J. Natl. Cancer Inst.* **96**:604-615.

18. Elbasha, E.H., Dasbach, E.J., and Insinga, R.P. 2007. Model for assessing human papillomavirus vaccination strategies. *Emerg. Infect. Dis.* **13**:28-41.

19. Spurgeon, S.A., Johnson, D., Pefole, M., and Fleishman, V. 2006. Challenges in Vaccine Policy: A Case Study of the HPV Vaccine. *New England Healthcare Institute Innovation Series.*

20. Ries, L.A.G., Melbert, D., Krapcho, M., Mariotto, A., Miller, B., Feuer, E.J., Clegg, L., Horner, M., Howlader, N., Eisner, M. et al. 2006. SEER Cancer Statistics Review, 1975-2004, Cancer of the Cervix. **2008**.

21. Brabin, L., Roberts, S.A., and Kitchener, H.C. 2007. A semi-qualitative study of attitudes to vaccinating adolescents against human papillomavirus without parental consent. *BMC Public Health 7:20* **7**:20.

22. Constantine, N.A., and Jerman, P. 2007. Acceptance of human papillomavirus vaccination among Californian parents of daughters: a representative statewide analysis.[see comment]. *J Adolesc Health 40(2):108-15* **40**:108-15.

23. Kahn, J.A. 2007. Maximizing the potential public health impact of HPV vaccines: a focus on parents.[comment]. *J Adolesc Health 40(2):101-3* **40**:101-3.

24. Brabin, L., Roberts, S.A., Farzaneh, F., and Kitchener, H.C. 2006. Future acceptance of adolescent human papillomavirus vaccination: a survey of parental attitudes. *Vaccine 24(16):3087-94* **24**:3087-94.

25. Colgrove, J. 2006. The ethics and politics of compulsory HPV vaccination. *N Engl J Med 355(23):2389-91* **355**:2389-91.

26. Lazcano-Ponce, E., Rivera, L., Arillo-Santillan, E., Salmeron, J., Hernandez-Avila, M., and Munoz, N. 2001. Acceptability of a human papillomavirus (HPV) trial vaccine among mothers of adolescents in Cuernavaca, Mexico. *Arch. Med. Res.* **32**:243-247.

27. Dempsey, A.F., Zimet, G.D., Davis, R.L., and Koutsky, L. 2006. Factors that are associated with parental acceptance of human papillomavirus vaccines: a randomized intervention study of written information about HPV. *Pediatrics 117(5):1486-93* **117**:1486-93.

28. Davis, K., Dickman, E.D., Ferris, D., and Dias, J.K. 2004. Human Papillomavirus Vaccine Acceptability Among Parents of 10- to 15-Year-Old Adolescents. *Journal of Lower Genital Tract Disease* **8**:188-194.

29. Olshen, E., Woods, E.R., Austin, S.B., Luskin, M., and Bauchner, H. 2005. Parental acceptance of the human papillomavirus vaccine. *J. Adolesc. Health* **37**:248-251.

30. Mays, R.M., Sturm, L.A., and Zimet, G.D. 2004. Parental perspectives on vaccinating children against sexually transmitted infections. *Soc. Sci. Med.* **58**:1405-1413.

31. Udesky, L. 2007. Push to mandate HPV vaccine triggers backlash in USA. *Lancet 369(9566):979-80* **369**:979-80.

32. Charo, R.A. 2007. Politics, parents, and prophylaxis--mandating HPV vaccination in the United States. *N. Engl. J. Med.* **356**:1905-1908.

33. Gostin, L.O., and DeAngelis, C.D. 2007. Mandatory HPV vaccination: public health vs private wealth. *JAMA* **297**:1921-1923.

34. Bleakley, A., Hennessy, M., and Fishbein, M. 2006. Public opinion on sex education in US schools. *Arch. Pediatr. Adolesc. Med.* **160**:1151-1156.

35. Singer, D.C., and Davis, M.M. May 2007. Majority of U.S. Parents Not in Favor of State HPV Vaccine Mandates. *C.S. Mott Children's Hospital National Poll on Children's Health* **1**.

36. Slomovitz, B.M., Sun, C.C., Frumovitz, M., Soliman, P.T., Schmeler, K.M., Pearson, H.C., Berenson, A., Ramirez, P.T., Lu, K.H., and Bodurka, D.C. 2006. Are women ready for the HPV vaccine? *Gynecol Oncol 103(1):151-4* **103**:151-4.

37. Kahn, J.A., Rosenthal, S.L., Hamann, T., and Bernstein, D.I. 2003. Attitudes about human papillomavirus vaccine in young women. *Int J STD AIDS 14(5):300-6* **14**:300-6.

38. Melnikow, J., Nuovo, J., Willan, A.R., Chan, B.K., and Howell, L.P. 1998. Natural history of cervical squamous intraepithelial lesions: a meta-analysis. *Obstet. Gynecol.* **92**:727-735.

39. Ostor, A.G., and Mulvany, N. 1996. The pathology of cervical neoplasia. *Curr. Opin. Obstet. Gynecol.* **8**:69-73.