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Economic Evaluation Of Implementing Hpv Vaccine Promotion Interventions For Cervical Cancer In The United States

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ECONOMIC EVALUATION OF IMPLEMENTING HPV VACCINE PROMOTION INTERVENTIONS FOR CERVICAL CANCER IN THE UNITED STATES

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The HPV vaccine has been proven as a safe and effective method for preventing cervical cancer. However, the HPV vaccine coverage rate in the U.S. is suboptimal. Various interventions have been implemented to improve HPV vaccine coverage. However, evidence of the cost-effectiveness of HPV vaccine promotion interventions is lacking. We conducted an economic evaluation to assess HPV vaccine promotion interventions of cervical cancer in the U.S. Firstly, a systematic review was conducted to review evidence on interventions aimed at increasing HPV vaccine coverage and to summarize the cost and effectiveness of these interventions. We included 56 HPV vaccine promotion studies in the review. Intervention approaches used to promote the HPV vaccine included patient reminder and recall systems (N=12), patient education (N=16), provider assessment and feedback (N=1), provider reminder (N=2), reducing out-of-pocket costs (N=3), school-based vaccine programs (N=4), vaccination requirements for school attendance (N=3), and intervention combinations (N=14). We also identified 7 studies that reported intervention costs. Most interventions significantly increased HPV vaccine rates using varied approaches across populations and settings, and with modest cost. The cost-effectiveness analysis is needed to determine which intervention type is the most cost-effective.

Secondly, we assessed the cost-effectiveness of several U.S. HPV vaccine promotion interventions versus current practice. Interventions of patient reminder and recall system, patient education, provider reminders, reducing patient out-of-pocket costs, school-based vaccine programs, and community-based intervention combinations were included in the evaluation. We found that patient reminder and recall system is the most cost-effective HPV vaccine promotion intervention. The cost per additional individual that completed HPV vaccine series (ICER) was $238. When the intervention effectiveness was measured as the percentage change of receiving at least one dose HPV vaccine, the ICER for the patient reminder and recall system was $107. A cost-utility analysis was conducted to assess HPV vaccine promotion interventions on cervical cancer in the U.S. The study shows that implementing patient recall and reminder system is the most cost-effective intervention for cervical cancer. Compared with current practice, patient recall and reminder system is cost-saving since the cost is lower and yields a better health outcome. Decision-makers need to consider the applicability of interventions and budgets for implementing the interventions. Social and political issues need to be discussed by stakeholder groups before HPV vaccine promotion interventions are successfully implemented.

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BACKGROUND

In 2019, nearly 13,000 women in the United States were newly diagnosed with cervical cancer (0.7% of all new cases of female cancers) and more than 4,000 women (0.7% of all cancer deaths) died from the disease.[1] The majority of cervical cancers are caused by human papillomavirus (HPV). Anyone who has ever been sexually active has a chance of being infected with HPV. In the U.S., more than 80% of sexually active individuals are expected to become infected with HPV at some point in their lives.[2] This highlights the importance on preventing the HPV infections in the US.

The HPV vaccine has been proven as a safe and effective method for preventing HPV transmission. However, the vaccine's coverage rate in the U.S. has been relatively low compared to coverage in other developed countries. According to recent data estimates, the up-to-date HVP vaccine coverage in 2017 was 48.6% among adolescents aged 13-17 years.[3] This coverage is far below the CDC's Healthy People target of 80% coverage by 2020. In comparison to 2017 coverage rates in other developed countries, the HPV vaccine coverage among females aged 12-13 years was 90% in the United Kingdom[4] and 85% for females at age 15 in Australia.[5] Implementing HPV vaccine promotion interventions is the accepted approach to increasing vaccination coverage. However, because there are many different ways to implement intervention, it is hard to determine which intervention method is the most cost-effective for increasing that coverage. A systematic review that summarizes and quantifies the impact of the current published HPV intervention methods can help enable healthcare professionals to evaluate the entire spectrum of interventions.

Previous studies have focused on the economic evaluations of HPV vaccine programs in relation to preventing cervical cancer.[6] However, those studies have typically failed to include the resources consumed by the interventions themselves, which may have biased the estimates of HPV vaccine program's health and economic impacts. To more realistically reflect the overall impacts of HPV vaccination programs, the costs of resources involved in the intervention strategies designed to improve coverage rates should also be incorporated in the economic evaluation research. For this present study, a systematic literature review was conducted to identify the cost-effectiveness of different HPV vaccine promotion interventions. We then incorporated synthesized evidence about intervention cost and effectiveness into the HPV vaccine economic evaluations to understand their impacts on HPV transmission preventions.

Epidemiology of cervical cancer

From the latest data released by the Centers for Disease Control and Prevention (CDC), the incidence of cervical cancer in the U.S. was 7.7 per 100,000 women in 2016. The mortality rate of cervical cancer was 155.9 per 100,000 women in 2016.[7] Both the incidence and mortality rate of cervical cancer have decreased over time (Figure 1).[7] This decline has resulted mainly due to cervical cancer screening of the majority of women in the U.S. In 2015, approximately 80% of women aged 21-65 years old received cervical cancer screening (Figure 2).[8] Because of the screening, the cancer can be found earlier and patients can be treated in the early stage.

Although both incidence and mortality rates of cervical cancer were declined among women diagnosed with cervical cancer from 2010 to 2015, more than 72% of them were younger than 60 years old. We found that the prevalent age of cervical cancer is younger, compared with top ranking female cancers including breast and ovary cancer. From 2010 to 2015, the percentage of women younger than 60 years old diagnosed with breast cancer and ovary cancer were 37.62% and 44.80% in the US, respectively (Figure 3) [7]. This highlights the importance of works in cervical cancer prevention.

Figure 1. Incidence and mortality of cervical cancer from 1999 to 2016 in the U.S.

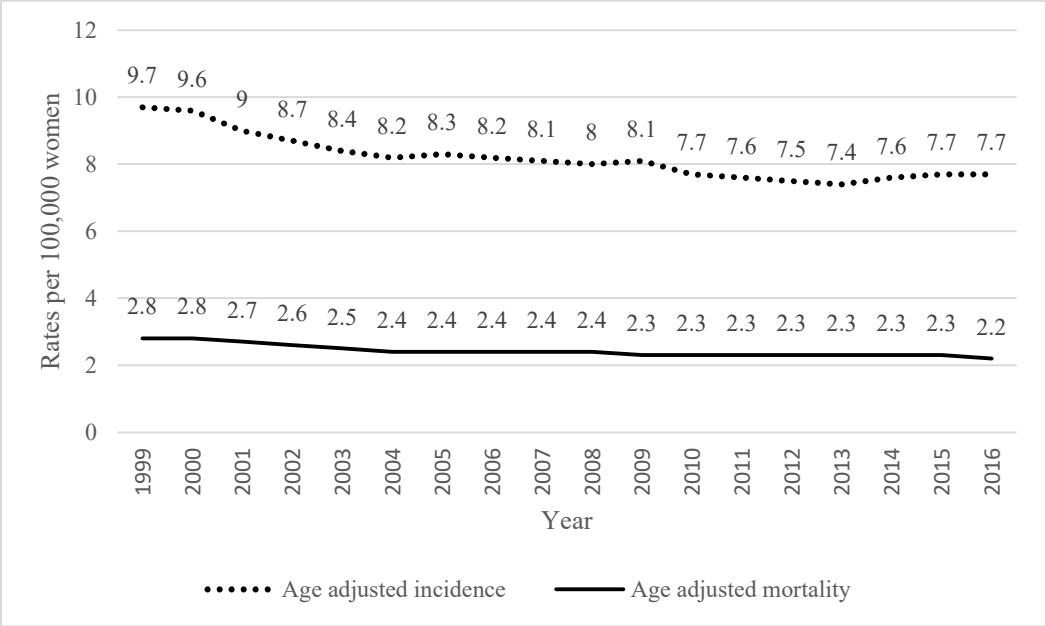


Figure 2. Percentage of women aged 21-65 years old receiving cervical cancer screening from 2000-2015 in the U.S.

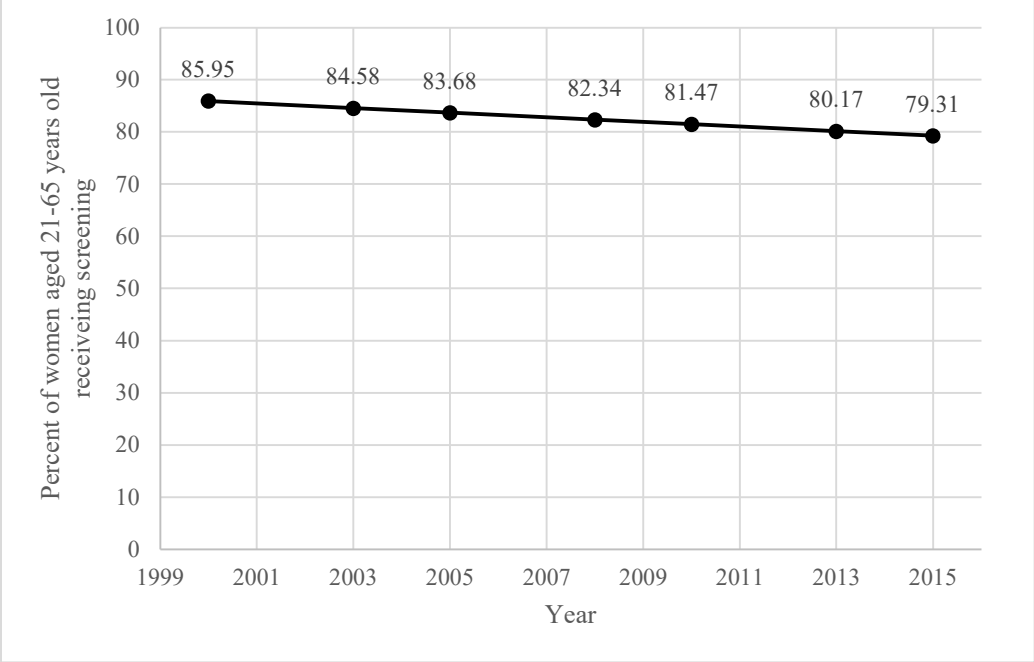
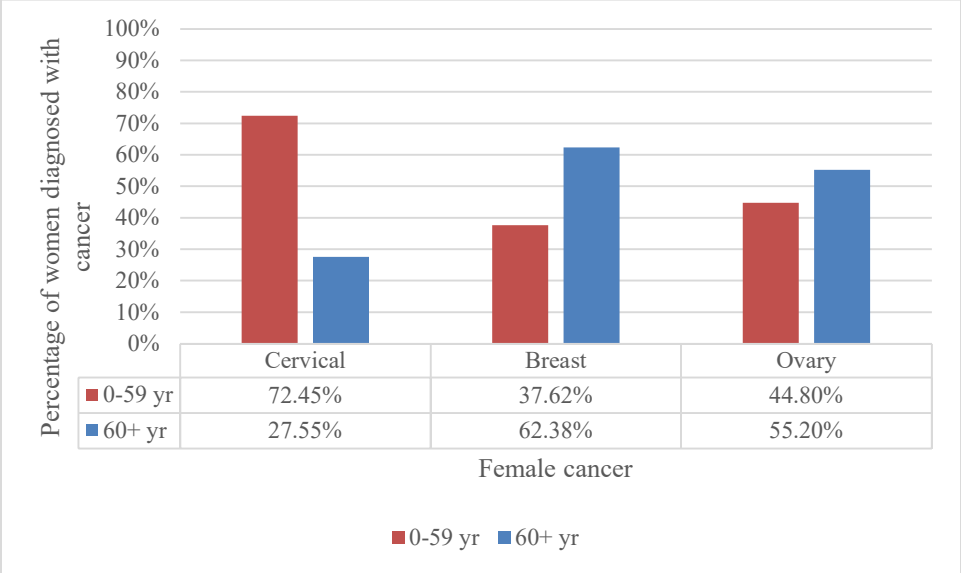


Figure 3. Percentage of women diagnosed with cervical, breast and ovarian cancer in the U.S. from 2010 to 2015



HPV vaccine access, utilization and policy in the U.S.

The HPV vaccine was approved by the Food & Drug Administration (FDA) in 2006 and recommended as standard coverage by enrolled health insurance plans, without increasing consumer cost-sharing. For individuals lacking access to private insurance, the vaccine can be covered through the following public-financed sections.[9,10]

1. Vaccines for Children (VFC) Program

   The VFC is a federally-funded program that provides HPV vaccines through the CDC to individuals younger than 19 years of age. Under the VFC program, there is no charge for the HPV vaccine for eligible children including Medicaid eligibilities, uninsured or underinsured individuals, and American Indians or Alaska Natives.

2. Immunization Grant Program (Section 317)

   Section 317 of the Public Health Service Act authorizes the federal government to purchase vaccines for distribution. It extends HPV vaccine access to underinsured children who are not eligible for coverage under the VFC and for uninsured adults.

3. Medicaid

   Individuals under age 21 who are enrolled in the Medicaid program are eligible for Medicaid's Early and Periodic Screening, Diagnostic and Treatment (EPSDT) coverage for the HPV vaccination.

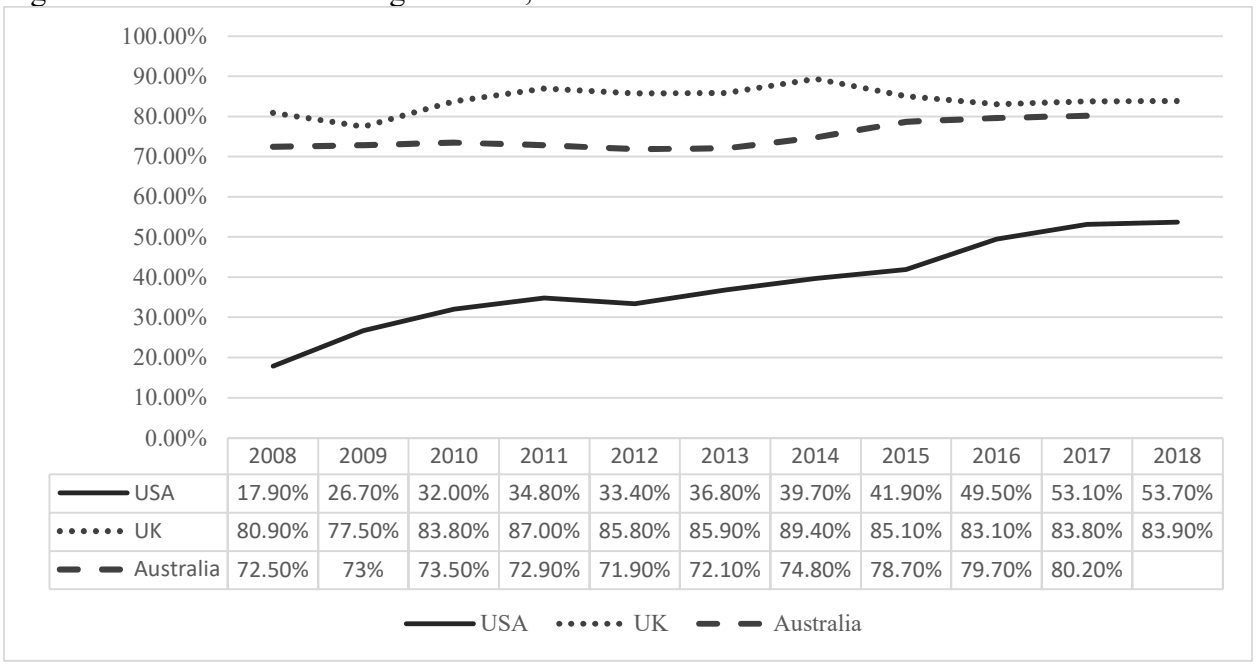
4. Children's Health Insurance Program (CHIP)

   CHIP is intended to provide coverage for uninsured children in families whose income is too high to qualify for Medicaid but who can not afford the private coverage. For children who are not eligible for VFC, Medicaid CHIP is a possible source for HPV vaccine access.

In 2007 following the first year of its FDA approval, the HPV vaccine's coverage rate was 5.9%; by 2018, the rate had increased to 53.7% (Figure 4).[11–13] Compared to rates in other developed countries including United Kingdom and Australia, HPV vaccine coverage in the U.S. is relatively low. The 2018 HPV vaccine coverage rates were 83.8% (2-dose) among females aged 13-14 years old in the United Kingdom.[12] In Australia, the HPV vaccine coverage among 15 years old females was 80.2% in 2017.[13] Both countries offered free HPV vaccines to males and females starting at age 12 years through national HPV vaccine programs. In the U.S., policies for HPV vaccination vary by state. State-based policies for improving HPV vaccination can be categorized as follows: 1) mandated vaccine for females; 2) mandated vaccine for males; 3) public funding offered; 4) mandated private health-insurance coverage of vaccine; 5) provided for vaccine-information delivery; 6) provided HPV-related awareness campaign; 7) bill supporting voluntary vaccination; 8) political backlash and/or mandate-reversal bill; and 9) others.[14] Since the initial 2006 policy approval in the U.S., 28 states have introduced bills regarding the HPV vaccine mandate to their legislatures, and three jurisdictions now require HPV vaccines for school attendance: Virginia, Rhode Island, and the District of Columbia. Most of the policy implementation across states has focused on awareness campaigns, vaccine information, ensuring private coverage, and public funding.[14] Because each state has different policies toward HPV vaccination, the coverage rates also vary by state. North Dakota had the highest HPV vaccine completion rate among girls aged 13-17 years in 2018 (52.8%), and Mississippi had the lowest vaccine coverage (23.4%) among stated without school mandate requirements.[11]

While three states currently have a school mandate requirement for HPV vaccination, the impact of the policy on uptake and completion is unknown. The National Immunization Survey-Teen (NIS-Teen) data shows the 2018 HPV vaccine 3-dose coverage rates among females aged 13-17 in Rhode Island, Virginia, and D.C. were 54.5%, 48.0%, and 58.3%, respectively.[11] We found that even with this HPV vaccine school entry requirement, the coverage is far below the Health People target for 2020. Based on NIS-Teen data for 2009-2013, our study also found that states with school mandates did not have higher HPV vaccine rates among females aged 13-17 years compared to states without school mandates. Provisions for religious exception, personal belief exemptions, and liberal opt-outs to the HPV vaccination may in fact weaken the school mandates impact.[15] Since the impact between mandate implementation and HPV vaccine coverage is not clear, implementing intervention programs is a critical way to increase the HPV vaccine coverage.

Figure 4. HPV vaccine coverage in USA, UK and Australia



	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
USA	17.90%	26.70%	32.00%	34.80%	33.40%	36.80%	39.70%	41.90%	49.50%	53.10%	53.70%
UK	80.90%	77.50%	83.80%	87.00%	85.80%	85.90%	89.40%	85.10%	83.10%	83.80%	83.90%
Australia	72.50%	73%	73.50%	72.90%	71.90%	72.10%	74.80%	78.70%	79.70%	80.20%	

HPV vaccine promotion interventions in the U.S.

The Community Guide's reports concluded the following interventions have been used to promote immunization rates, including patient reminder and recall systems, patient education, provider assessment and feedback, provider reminders, vaccination requirements for school attendance, vaccination programs in schools, reducing out-of-pocket costs, standing orders, immunization information systems and multiple component interventions (interventions implemented in combination involved more than two interventions). However, conclusions about the most effective HPV vaccine promotions were heterogeneous across the studies. One study found that population-based vaccination strategies that consistently reached the greatest number of participants, such as school-based vaccination programs were the most successful at reaching a high HPV vaccine uptake rate.[16] Another systematic review suggests that those interventions designed in combination for both the community and the provider have been the most effective in terms of increasing the uptake rate.[17] A systematic review that identified evidence of educational interventions of the HPV vaccine concluded there is no strong evidence to recommend any particular educational intervention to achieve high uptake rates.[18] Given these results, it's clear additional studies of HPV vaccine intervention methods are needed in order to identify the most effective approach.

Cost is also an important element when evaluating intervention methods. However, evidence about the cost of HPV vaccine promotion intervention is limited. Most of the intervention studies we reviewed did not report cost results for implementing the intervention. From those studies which did, the units were heterogeneous across studies, making it difficult to compare costs between and among different intervention approaches. For example, one study applying

the provider assessment and feedback approach reported the cost per child vaccinated.[19] In another, the cost per vaccine administered in a school vaccination program was used.[20] Additional cost studies and synthesized results are needed to create the basis for a better understanding.

Economic evaluation for HPV vaccination in the U.S.

We reviewed published economic evaluation studies about HPV vaccine program which showed consistently that HPV vaccine program is cost-effective in in preventing HPV-associated cancers, compared with currently standard programs.[6] Chesson et al. assessed the cost-effectiveness of HPV vaccination in the U.S. of 12-year-old females. Their results show that the HPV vaccine was more cost-effective at preventing cervical cancer compared with the current screening policy. The estimated cost per quality-adjusted life year (QALY) ranged from $3,906 to $14,723.[21] Approximately 70% of cervical intraepithelial neoplasia (CIN) and 20% of cervical cancers were found to be preventable by implementing the HPV vaccine. In a 2007 study, Elbasha et al. assessed the epidemiologic consequences and cost-effectiveness of HPV vaccination among 12-year-old females. They found the HPV vaccination was cost-effective, with an incremental cost-effective ratio (ICER) averaging $4,666 per QALY compared with no vaccination. They concluded that vaccinating girls younger than 12 could reduce the incidence of genital warts (83%) and cervical cancer (78%) resulting from HPV infections. Overall, HPV vaccination is cost-effective when compared with currently accepted programs which prevent HPV-related outcomes.[6]

While HPV vaccination has been shown as a cost-effective method of cancer prevention, our findings indicate that the majority of economic evaluations addressing HPV vaccination have assumed an HPV vaccine coverage rate of up to 70%. For example, both Chesson et al. and Elbasha et al. assumed the HPV 3-dose coverage increased linearly from 0% to 70% during the first five years of the program and remained at 70% thereafter.[21,22] Because the current vaccine coverage rate is closer to 50% in the U.S., the reviewed published results might exhibit

some bias with that assumption. Implementing HPV vaccine promotion intervention is a main approach to increase HPV vaccination rates. Future study should also consider the element of the cost for any HPV vaccine promotion intervention designed to increase the HPV vaccine coverage into the evaluation study.

Public Health Significance

In the U.S., the national and state-wide rates of HPV vaccine coverage are relatively low. Interventions aimed at increasing HPV vaccine coverage are the main way to address this concern. Because there are many factors involved in designing interventions, it is important to understand what types of intervention are the most cost-effective. Furthermore, the costs for developing and implementing these interventions should be included when conducting an economic evaluation of the HPV vaccine program. In this study, a systematic review was conducted to identify the evidence of HPV vaccine promotion interventions in the U.S. Secondly, a cost-effectiveness analysis was conducted to identify what types of intervention are the most cost-effective. The third aim is to incorporate the element of HPV vaccine promotion intervention in the economic evaluation of HPV vaccine programs. This information can provide evidence for policymakers when developing plans and policies related to the administration of HPV vaccines.

Hypothesis, Research Question, Specific Aims or Objectives

The overall objective of this study is to conduct an economic evaluation of the implementation of HPV vaccine promotion interventions. The study's specific aims are:

1. To identify evidence extracted from the existing literature that directly addresses interventions aimed at increasing HPV vaccine coverage;
2. To assess the cost-effectiveness in terms of increasing HPV vaccine coverage of the most effective HPV vaccine promotion intervention in the U.S.;
3. To assess the cost-utility in terms of QALYs gained by implementing the most effective HPV vaccine promotion intervention in the U.S.

METHODS

Study Design

We first conducted a systematic review to identify the evidence related to interventions aimed to increase the HPV vaccine coverage. The most cost-effective intervention strategy, relative to the standard intervention, was identified using CEA. A cost-utility analysis (CUA) was then developed to assess the life-years gained and QALYs gained after implementing the HPV vaccine promotion interventions, compared with the standard intervention.

Data Collection

To identify evidence related to HPV vaccine promotion interventions, we searched MEDLINE and PubMed to identify studies of interventions published during the period 2007 to 2017. Studies were included if the stated outcome was measured quantitatively as HPV vaccine coverage rates. Study methods, intervention types, and results were extracted from the included studies. For the data needed for the CUA study, we derived them from published literature.

Human Subjects, Animal Subjects, or Safety Considerations

The IRB submission requirement was waived as this study used only published literature for its data collections.

JOURNAL ARTICLE - 1

Systematic reviews of evidence regarding interventions designed to increase HPV vaccine coverage

American Journal of Preventive Medicine

Background

Nearly 44,000 cases of HPV-associated cancer were diagnosed in the U.S. each year between 2012 and 2016, and research data indicates that approximately 73% of these cases were preventable through HPV vaccination.[1] The safety and effectiveness of the HPV vaccine have been proven in clinical trials. The vaccine series is recommended by the CDC for all adolescents starting at age 9 up through 26 years.[2] However, HPV vaccine coverage in the U.S. is low. According to the most recent data, only 53.7% of girls aged 13-17 years were up to date with the HPV vaccine series in 2018.[3] This coverage rate is far below the CDC's Healthy People target of 80% coverage by 2020. Underuse of the vaccine means that adolescents miss an important opportunity to protect themselves against HPV-associated cancers. To increase the vaccine's coverage rate, implementing HPV vaccine promotion intervention is fundamental. However, the strategies for these interventions are often heterogeneous, which makes it's challenging to determine the impact of those interventions. Furthermore, the resources, such as costs of implementations varied across interventions and evidence of it is little. A review that quantifies the intervention impact and identifies resources to implement HPV vaccine promotion interventions is needed. We found a 2016 systematic review that summarized evidence including intervention outcomes and costs of 34 HPV vaccine promotion interventions.[4] They found that many most of the interventions can significantly increase the

HPV vaccine coverage rates with modest costs. In our review, we have updated their results which incorporated more recent studies and included all intervention techniques recommended by the Community Guide (an independent literature review panel made up of public health and prevention experts) for promoting vaccine coverage. In this systematic review, we presented and summarized the results of the cost and effectiveness of the HPV vaccine promotion interventions.

Methods

We used the Community Guide categorizing system to categorize intervention approaches which included in our review. The Community Guide has identified the following intervention approaches are used to promote immunization rates, including home visits, school requirements, patient-held paper immunization records, patient/provider education, monetary sanction policies, patient reminder and recall systems, provider assessment and feedback, provider reminders, vaccination requirements for school attendance, vaccination programs in schools, reducing out-of-pocket costs, standing orders, immunization information systems, and multiple components interventions (combined two or more intervention strategies).[5] MEDLINE and PubMed were used to identify the published intervention methods intended to increase HPV vaccine coverage during the period from 2007 to 2017. Three key Medical Subject Heading (MeSH) terms were used for the search: 'human papillomavirus', 'vaccine', and 'intervention'. Details for searching keywords are listed in Table 1 of the Appendix. All the relevant search literature was imported to RefWork (ProQuest) for citation management, data selection, and duplicate checks. All the studies were screened by title and abstract to ensure they qualified for inclusion. The eligibility criteria for inclusion and exclusion criteria

are listed in Table 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used as a guideline for conducting the review study. Extracted data included these elements: author, year of publication, intervention participant characteristics including age and gender, study sample size, intervention design, intervention setting, outcome measurements and results, and intervention costs.

Meta-analysis was used to estimate the summarized effectiveness of each intervention strategy. We assessed the outcome of the HPV vaccine completion rate which was measured as the difference of the 3-dose HPV vaccine rate between the intervention and control groups. A forest plot of effectiveness for the HPV vaccine promotion intervention was constructed. Heterogeneity was assessed using I-squared (I^2); an $I^2 \leq 25\%$ is considered minimal, 26% to 74% is moderate and $\geq 75\%$ is excessive heterogeneity. All analyses were performed using STATA (Stata, Release version 15).

Results

The literature selection process is presented in Figure 5. From among the initially identified 1,782 unique articles, 56 were included in the review. The characteristics of the studies included in the review are presented in Table 2. Intervention approaches used to improve HPV vaccine coverage included patient reminder and recall systems, patient education, provider assessment and feedback, provider reminders, reducing out-of-pocket costs, school-based vaccine programs, vaccination requirements for school attendance, standing orders, immunization information systems and multiple component interventions (interventions implemented in combination involved more than two interventions). The age of the study population ranged from 9 to 29 years old. In the review, 55.4% (N=31) of the

interventions focused exclusively on females.[6,7,16–25,8,26–35,9,36,10–15] There were 11 studies focused on specific populations, including low-income,[11,37] Korean-American,[9] African-American,[13] Haitian-American and African-American,[18] Hispanic and African-American,[38] Appalachian,[19,22,24] women who served in the military,[20] and Mexican-American.[39]

Effectiveness of interventions: Background and results

Patient reminder and recall system

Background: Under the patient reminder and recall system approach, members of the target population are reminded if an HPV vaccination is due or late. Reminders and recalls are delivered through various methods, including text messaging, prerecorded voice messages, postcards, E-mail, telephone calls or standard mailed letters.[40]

Evidence on effectiveness: We found 12 interventions (21.4%) used a patient reminder and recall system to increase HPV vaccine coverage.[7,8,45,46,9–11,37,41–44] Reminder and recall are delivered by various methods, including text, voice message, postcard, mailing letter, telephone call from the patient navigator, E-Mail and social media message. Interventions were provided by health care providers, such as primary care providers or pediatricians. For the study design, three were pre- and post-intervention studies [9,11,46] and nine were intervention and control interventions.[7,8,10,37,41–45] Among nine intervention and control studies, seven included randomization[7,10,37,41–44] and two are not randomization interventions.[8,45] For the outcome measure of the intervention, two measured HPV vaccine series initiation,[42,45] six measured series completion,[7,10,37,41,43,44] and one study measured both initiation and completion rates.[11] Two studies measured the percentage of receiving an HPV vaccine dose[9,46] and one study measured the percentage of receiving the next HPV vaccine.[8] Among studies comparing

HPV vaccine series completion rate between intervention and control groups, the rate ranged from -1.7% to 25% (median increase of 7.3%). One study found that the HPV vaccine series completion rates of the mailed reminder, telephone reminder and standard care were 18%, 19% and 14%, respectively.[37] Another study compared the series completion rates involving the use of telephone reminders versus text messages versus standard care; data indicated the telephone reminder intervention resulted in an 8% increase over that of standard care, while the use of text reminders resulted in an 18% increase compared to standard care.[43] Another study showed intervention methods resulted in a 25% increase compared with usual care.[44] In one 2014 study, they found that the HPV vaccine series completion rate was lower by 1.7% in the intervention group as compared to that of the control group. [10]

Evidence on economic: Three studies were included in the economic review (Table 3)[37,42,46]. One study estimated the cost of sending automated text, prerecorded voice, and postcards to parents. Costs reported in the study were <$0.10 and $1.50 per automated message and per postcard sent, respectively[46]. Another study estimated total operating costs, including personnel and supply cost, of reminder and recall for immunizing adolescents in four private pediatric practices. The total operating costs among the four practices ranged from $1,087 to $1,349[42]. In Szilagyi et al. study, they conducted a randomized controlled trial of a managed care-based patient reminder and recall system. They estimated the intervention costs were $18.78 and $16.68 per adolescent per for mailed letter and telephone reminders, respectively[37].

Patient education

Background: The patient education approach provides accessible information to the target populations and intends to change their attitudes about HPV vaccination. It is delivered

via various methods such as online education intervention, written information (e.g. brochure, posters, and news releases), educational videos, and educational curriculum content.[47,48]

Evidence on effectiveness: Patient education is the most common approach used to increase HPV vaccine coverage. Our search identified sixteen studies used patient education to increase HPV vaccine coverage (28.6%)[6,12,38,49–53,13–20] Six were pre- and post-intervention studies, [16,20,49–52] while others were intervention and control studies.[6,12–14,17–19,38,50,53] A majority of studies were conducted in health clinical settings (N=10). Effectiveness measurements were heterogeneous across literature, including HPV vaccine initiation rate (N=5),[14,20,49,50,53] HPV vaccine completion rate (N=4),[13,18,19,38] number/percentage of participants receiving an HPV vaccine dose (N=4), [15,16,51,52] number/percentage of participants receiving a needed HPV vaccine among who already initiated the first dose (N=2) [6,17] and the cumulative HPV vaccination rate (N=1).[12]

Results for the HPV vaccine series completion rate varied widely across the studies. Among studies comparing HPV vaccine series completion rate between intervention and control groups, the rate ranged from -5.6% to 11.4% (median increase of 3%). In Sanderson et al. (2017) study, the intervention consisted of two elements: provider/staff training sessions and provision of patient educational materials included a video and a flyer promoting HPV vaccine. After the intervention, the HPV vaccine completion rate was lower in the intervention group versus the control group (12.4% versus 18.0%).[38] Another study applied a client-centered behavioral health education curriculum to the intervention technique, and results show the HPV vaccine completion rate was slightly higher but not significantly in the intervention group than the control group (10% versus 7%).[18] Vanderpool et al. examined the

effectiveness of an educational DVD intervention to promote HPV vaccine. After the intervention, they found that 43.3% of the women randomized to the intervention group completed 3 dose HPV series, whereas 31.9% of women in the control group completed the series. [19]

Evidence on economic: One study was identified which provided evidence on cost (table 3)[54]. An education session was implemented using the print-based photonovella intervention and iPad-based tailored interactive multimedia tool (TIMI) among Hispanic parents. The study estimated costs by using print-based photonovella intervention and TIMI were $88 and $108 per participant, respectively.

Vaccination requirements for school attendance

Background: HPV vaccination requirements are a response to legal rules or policies that require adolescents attending a school to be vaccinated with HPV immunization as a condition for school entry. Vaccination requirements vary across states according to comprehensiveness, acceptable documentation of immunity, access to exemptions, and the type and consistency of enforcement.[55]

Evidence on effectiveness: Three studies examined the effect of school entry requirements and HPV vaccine coverage.[28–30] Moss et al. compared the HPV vaccine series initiation rate between states that had and had not adopted school entry vaccination requirements; they found that states with the HPV vaccination requirement had a <1% increase in the series initiation rate compared to that for states without the HPV vaccine requirement (47.7% vs 47.3%).[28] Another study found that states with either school-entry or education mandates do not have higher HPV vaccine series completion rates compared to rates in states

without such mandates.[29] Potter et al. focused on the effect of Michigan's school rule enacted in 2010 that the HPV vaccine must be initiated for females. They found that the HPV vaccine series initiation rate in females aged 13 enrolled in sixth grade after 2010 increased less than 5% over that for females enrolled before the requirement was implemented.[30] Results from the three studies were consistent in demonstrating that HPV vaccine coverage was not significantly different before and after the vaccination requirement.

Evidence on economic: No economic evidence of vaccination requirements for school attendance was identified.

Provider assessment and feedback

Background: Provider assessment and feedback retrospectively assesses provider performances about HPV vaccine delivery to a target population. Feedback may involve other components such as benchmarks or incentives.[56]

Evidence on effectiveness: One study used provider assessment and feedback as a way to improve HPV vaccine coverage. Perkins et al. found that the HPV vaccine series completion rate increased to approximately 60% in both female and male case groups.[57] They concluded that provider assessment and feedback have the potential to improve HPV vaccination rates, yet more evidence is needed to fully assess the effects of the intervention.

Evidence on economic: No economic evidence of provider assessment and feedback was identified.

Provider reminders

Background: Provider reminders inform those who administer the HPV vaccines know that patients are due for a vaccination. Provider reminders are delivered in various ways,

including notes or alerts posted in patients' charts or electronic medical records, or letters sent by mail or e-mail.[58]

Evidence on effectiveness: Two studies used provider reminders to promote the HPV vaccine.[21,59] They incorporated HPV vaccination reminders into electronic medical records or reminder sheets for health care providers. Soon et al. found that the HPV series initiation rate increased significantly between pre- and post-intervention (from 1.2% to 26.5%).[21] However, Szilagyi et al. measured the HPV series completion rate and found that provider reminders failed to improve the rate, concluding that more rigorous practice-based changes are needed to promote the HPV vaccine.[59]

Evidence on economic: No economic evidence of provider reminder was identified.

Reducing client out-of-pocket costs

Background: Reducing client out-of-pocket costs involves programs that makes HPV vaccination more affordable. Implementations can include making substitute payments for vaccinations, providing insurance coverage, and lowering or eliminating patient out-of-pocket expenses.[60]

Evidence on effectiveness: Three studies used reducing out-of-pocket costs to promote the HPV vaccine.[22–24] A voucher was provided to participants to redeem three doses of the HPV vaccine at no cost. Two of the studies measured the HPV vaccine series initiation rate before and after the intervention among Appalachian females[22,24] The series initiation rate increased following intervention from 25% to 45%. The other intervention was implemented at a university health clinic, and the change in the HPV vaccine series completion rate was

measured before and after the intervention. Findings show that about 30% of the participants received all three doses of HPV vaccine following the intervention.[23]

Evidence on economic: No economic evidence of interventions designed to reduce client out-of-pocket costs was identified.

Vaccination program in schools

Background: Vaccination programs in schools are an intervention under which the HPV vaccine is delivered on-site to improve the immunization rate among the target population. The intervention involves multiple components: immunization education and promotion, assessment and tracking of vaccine status, referral of under-immunized students to vaccination providers, and the actual provision of the vaccines. [60]

Evidence on effectiveness: Four studies investigated the use of vaccination programs in school as a means to increase HPV vaccine coverage.[25–27,61] Three were implemented at the elementary and middle school level, and results showed increased series initiation rates ranging from 5% to 35%.[25,27,61] The fourth intervention was implemented at a university, and the HPV vaccine series completion rate was measured. After the intervention, the completion rate rose by almost 50% among the uninsured or underinsured students.[26]

Evidence on economic: Two studies were included in the economic review [25,27]. One study implemented a school-located adolescent vaccination program and estimated vaccine administration costs were $23.98 per vaccine dose [25]. Another study estimated total costs for implementing school-located HPV vaccination clinics in partnership with a local health department. The estimated total costs based on that study is 36% of the $376,104 budget, which is equivalent to $135,398 [27].

Multiple components interventions

Background: Multiple components interventions involve two or more types of intervention, such as the patient reminder and recall system plus patient education.

Evidence on effectiveness: Seven studies used the patient reminder and recall system plus patient education as a mean to promote the HPV vaccine.[10,31,32,39,62–64] Five studies measured the series completion rate[31,39,62–64] and two reported on the series initiation rate[10,32] for the HPV vaccine. Data addressing the results of the intervention effects were mixed. One study found the HPV vaccine series completion rate was not significantly different between measures of the intervention (34%) and the control (32%) groups.[62] Conversely, four studies found significant differences for the HPV vaccine series completion rate between the intervention and the control groups, with differences between them ranging from 13% to 55%.[31,39,63]

Two studies used the patient reminder and recall system plus the provider assessment and feedback method as a means to promote HPV vaccine.[34,65] This intervention combined reminder notifications for patients and feedback on immunization rates sent to providers. The vaccine series completion rate increased by about 10% in both the intervention and control groups.[65]

Two studies used patient education plus provider assessment and feedback as a means to improve HPV vaccination rates.[66,67] Results of this intervention's effectiveness were consistent in both studies. Findings indicate that the HPV vaccine series completion rate increased by approximately 10% to 20% with the intervention.

One study involved an intervention which combined three components: patient reminder and recall system, provider reminder, and provider assessment and feedback.[35] The researchers found that the HPV vaccine series completion rate was higher in the intervention group than in the control group by 10%. Another intervention that included three components (provider assessment and feedback, standing orders, and immunization information systems) found the HPV vaccine series completion rate increased by about 1% after intervention.[36] Farmar et al. investigated an intervention method incorporating provider reminders, standing orders, immunization information systems, and vaccination programs in school. Findings showed the HPV series completion rate was higher in the intervention group in comparison with national estimates.[68] As observed, results for the effectiveness of multiple-component intervention are mixed, and additional studies are needed for a better understanding.

Evidence on economic: One study was included in the economic review.[35] An intervention that combined provider education, electronic health record-based alerts and audit and feedback was implemented in primary care practices. Total costs for implementing the combined intervention were $9,946 to administer the HPV vaccine dose 1 to 3 [35].

Meta-analysis on summarized effectiveness of each intervention strategy

A meta-analysis was constructed to assess the outcome of the HPV vaccine completion rate of interventions. We identified 21 studies that reported the difference of the HPV vaccine completion rate between intervention and control studies. 5 studies were removed from the analysis since the information on either the number of intervention participants or the number of individuals completed the vaccine was not clear. [11,41,63,65,68] There were 24 intervention arms in 16 studies included in the meta-analysis. Interventions of patient reminder and recall system,

patient education, provider reminder, vaccination requirements for school attendance and intervention combination were included in the meta-analysis. Other interventions were excluded since the difference in HPV vaccine series completion rate between intervention and control groups was not available.

A forest plot, stratified by the intervention strategy, is shown in Figure 6. Overall, the percentage difference for increasing the HPV series completion between the intervention and control groups was 8.0% (p-value < 0.05, indicating a significant difference in the outcome between intervention and control groups). The highest summarized intervention effectiveness is intervention combination (16%), followed by the patient reminder (10%) and patient education (3%). For both the provider reminder and vaccination requirements for school attendance, the difference in HPV vaccine completion rate between intervention and control group was not statistically significant. We found that there was a great deal of heterogeneity of interventions ($I^2 = 96\%$), indicating a high heterogeneity among studies.

Discussion

The purpose of this study was to identify and summarize published evidence on interventions designed to increased HPV vaccine coverage in the U.S. We found 56 qualified studies regarding interventions aimed to increase HPV vaccine coverage. We then extracted data for the study population, intervention design, intervention results about changes related to the HPV vaccine coverage, and intervention costs where available. Several systematic review studies focusing on HPV vaccine promotion interventions were conducted, but the evidence is not comprehensive. Fu et al. conducted a systematic review that identified HPV vaccine promotion interventions, but they mainly focused on educational interventions.[69] In a 2015

study, Niccolai et al. included only interventions conducted at the practice or community level, including the patient reminder and recall system, physician-focused interventions, school-based programs, and multiple component interventions.[70] Other outcomes which are important when evaluating an intervention (such as costs) are not synthesized across studies. We identified interventions falling within the Community Guide's categories for in increasing vaccine coverage and documented both effectiveness and costs of interventions.

In the 56 qualified studies, patient education was identified as the most common approach used to promote the HPV vaccine (N=16). However, the conclusions for the intervention effectiveness were not consistent across the literature. In the Community Guide report which focused on interventions of other immunizations, they found that there is insufficient evidence to prove patient education is effective for promoting immunization. In Fu. et al. systematic review of HPV vaccine promotion intervention, they also concluded that there is no strong evidence to recommend patient education for implementation. [69] In our review, the outcome measurement in patient education intervention studies was diverse. It was difficult to directly compare outcome measures across studies. This suggests that there is a need for more intervention research.

We identified 12 interventions that use the patient reminder and recall system to promote the HPV vaccine. Using this approach to increase the vaccination rate is recommended by the Community Guide. Regardless of the type of reminder and recall used (e.g., text, email telephone), many studies indicated that the method generated a significant increase for the HPV vaccine initiation and completion rates.[7,37,42–45] Overall, we found an average increase of 10% in the HPV series completion rate after the intervention.

Four interventions for applying the vaccine program in a school setting were identified in the study. This intervention method is recommended by the Community Guide based on strong evidence of its effectiveness at increasing vaccine coverage. Three of the four studies measured the series initiation rate and found a significant increase in it following the intervention.[25,27,61] To better understand this intervention method's impact on HPV vaccine coverage, a study that measures the HPV vaccine series completion rate is needed in the future.

We found three articles which evaluated vaccination as a requirement for school attendance. This intervention practice is also recommended by the Community Guide for increasing vaccine coverage. However, none of the three studies included in our review found a significant increase in HPV vaccine coverage after implementing this intervention. We note that HPV vaccine awareness might differ from that of other adolescent vaccinations such as Tdap and MCV4. More research addressing the differences in vaccine acceptance is needed.

We identified seven studies that cost data are available. Making a conclusion for the intervention cost from included studies was challenging. Foremost, we found the information about cost needed for intervention implementation was limited across the literature. In addition, the methods of presenting intervention costs were heterogeneous across the included programs, such as cost per mailing sent[46] or cost per vaccine administered.[25] cost items reported in studies were diverse across the literature. For example, Karanth et al. reported detailed information on cost items including personnel, material and participant time.[54] In a study by Bar-shain et al., cost information given in the study was only the cost per message or mail sent.[46] We recognize that cost estimates might be biased if the information reported in the study was not comprehensive. We find that the cost of

implementing an intervention is an important element when designing the intervention, and further studies are needed to generate a better understanding.

One major limitation of this review was that many studies had limited generalizability in their results. Of the studies identified in this review, there was a high amount of variability between study populations and the intervention design. We found 11 studies focused on specific populations, such as low-income or African-American females. Readers should be cautious when generalizing results to the general population from rather selected groups. Some studies had small sample sizes or were pre-post study design, it is difficult to state conclusively for the intervention effectiveness. This review demonstrates the need for more studies with population-level samples and randomized designs to better quantify intervention impacts.

Conclusions

We included 56 HPV vaccine promotion studies in the review. Intervention approaches used to promote the HPV vaccine include patient reminder and recall systems (N=12), patient education (N=16), provider assessment and feedback (N=1), provider reminder (N=2), reducing out-of-pocket costs (N=3), school-based vaccine programs (N=4), vaccination requirements for school attendance (N=3), and intervention combinations (N=14). We also identified 7 studies that reported intervention costs. Most interventions significantly increased HPV vaccine rates using varied approaches across populations and settings, and with modest cost. The cost-effectiveness analysis is needed to determine which intervention type is the most cost-effective.

Table 1. Inclusion and exclusion criteria for the systematic review

Inclusion • Study design: Study has at least one comparison group to measure the differences or changes of the HPV vaccine coverage. • Intervention: Interventions designed to increase HPV vaccine coverage • Outcome: Post-intervention HPV vaccination coverage. The differences or changes must be reported and measured quantitatively.
Exclusion • Post-intervention HPV vaccination rate was not available or not reported quantitatively • No original data • Abstract or primary research only • Study is not available in English

Figure 5. Flowchart for selecting the literature

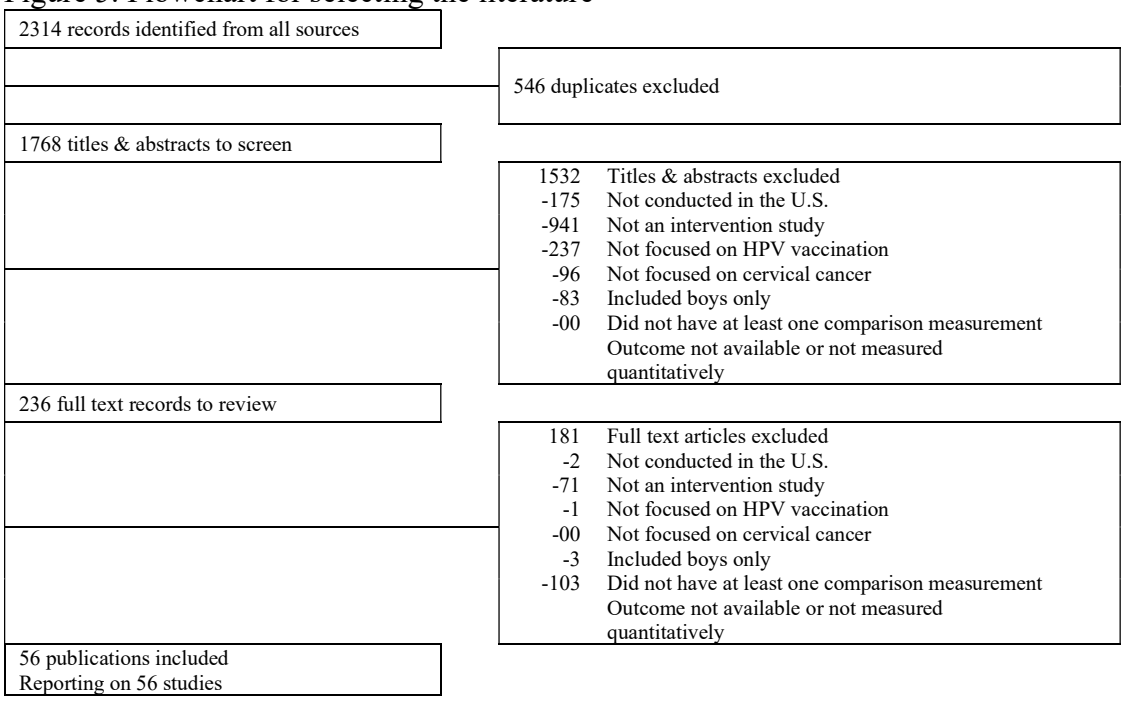


Table 2. The characteristics of studies included for the review

Author / year	Target population (age, gender, sample size)	Intervention (design, setting, intervention and control conditions)	Outcome (measurement, results)
Patient reminder and recall system (N=12)			
Bar-Shain et al. 2015 [46]	11-18 years old female and male, N= Parents/guardians of 3,393 patients	-Pre- and post-intervention: Immunization message reminder including automated text, prerecorded voice, and/or postcard -S: A large academic, tertiary, public health system	-Among patients who needed a vaccine, 22.9% received an HPV vaccine
Berenson et al. 2016 [11]	16-26 years old low-income postpartum female, N=1,038	-Pre- and post-intervention: Patient navigator and reminder program including text, mailing reminders and telephone call -S: Public hospitals	-Series initiation rate: increased from 25.4% before the intervention to 80.8% after the intervention. -Series completion rate: increased from 115.5% before the intervention to 65.1% after the intervention
Chao et al. 2015 [7]	9-26 years old female, N (I)=9,760; N(C)=2,445	-I: Reminder message and phone call for HPV vaccine schedule and follow-up visits to complete the vaccine -C: Standard care -S: The managed care organization Kaiser Permanente Southern California	-Series completion rates for all females aged 9-26 years old were 56.4% and 46.6% in I and C groups, respectively -Series completion rates for females aged 9-17 years old were 66.2% and 53.5% in I and C groups, respectively -Series completion rates by females aged 18-26 years old were 43.5% and 37.0% in I and C groups, respectively

Chung et al. 2015 [45]	11-18 years old female and male, N(I)=1 county; N(C)=4 counties	- I: Postcard reminder and school-generated telephone reminders -C: No intervention -S: Medical practice settings including family medicine practices, pediatric practices, and the county health department	-Series initiation rate for females aged 11-12 years old: improved by 27.4% to 43.4% in the intervention group -Series initiation rate for males aged 11-12 years old: improved by 14.2% to 32.1% in the intervention group
Kempe et al. 2016[44]	11-17 years old female and male, N(I)= 374; N(C)=555	-I: Preference-based recall including text, E-mail, auto-dialer and combined methods -C: Usual care -S: Kaiser Permanente Colorado Pediatrics practices	-The rate for receiving 2 doses from HER were 83% and 71% in I and C groups, respectively -Series completion rates from HER were 63% and 38% in I and C groups, respectively
Kharbanda et al. 2011 [8]	9-20 years old female, N(I)=124; N(C)=308	-I: Up to three weekly text message reminders -C: No text message reminder -S: Pediatrics clinics in New York City	-I: 51.6% of females received their next HPV vaccine dose -C: 35.0% of females received their next HPV vaccine dose
Lee et al. 2016 [9]	21-29 years old Korean-American female, N=30	-Pre- and post-intervention: 7-day text message HPV intervention	- 30% of participants received their first HPV vaccine dose
Patel et al. 2014 [10]	19-26 years old female, N(I)=180; N(C)=185	-I: Automated reminder message including text, E-mail, phone, private Facebook message, or standard mail -C: Usual follow-up -S: Outpatient reproductive health centers	-The rate for receiving 2 doses were 40.6% and 40% in I and C groups, respectively -Series completion rates within 32 weeks were 17.2% and 18.9% in I and C groups, respectively

Rand et al. 2015 [41]	11-16 years old female and male, N(I)=1,893; N(C)=1,919	- I: Text message reminder and recall system for HPV vaccination -C: General adolescent health text messages -S: Primary care practices	-Series initiation rates were 16% and 13% in I and C groups, respectively -The rate for receiving 2 doses were 7% and 6% in I and C groups, respectively -Series completion rates were 2% and 2% in I and C groups, respectively
Rand et al. 2017 [43]	11-17 years old female and male, N(I1)=178; N(C1)=180 N(I2)=191; N(C2)=200	-I1: Telephone reminder -C1: Standard care -I2: Text message reminder -C2: Standard care -S: Urban primary care clinics	-For phone reminder, series completion rates were 48% (85/178) and 40% (72/180) in I1 and C1 groups, respectively - For text reminder, series completion rates were 49% (93/191) and 31% (61/200) in I2 and C2 groups, respectively
Suh et al. 2012 [42]	11-18 years old female and male, N(I)=799; N(C)=797	-I: Reminder/recall for immunizing adolescents with 2 letters and 2 calls -C: Usual care -S: Private pediatric practices in metropolitan Denver	-Series initiation rate from Colorado Immunization Information System: -I: 26.5% -C: 15.3%
Szilagyi et al. 2013 [37]	11-17 years old low-income female and male, N(I1)=1,396; N(I2)=1,423; N(C)=1,296	-I1: Mailed letter -I2: Telephone reminder -C: Standard care -Primary care practices	-Series completion rates from insurance claims files: -I1: 18% -I2: 19% -C: 14%
Patient education (N=16)			

Bennett et al. 2015 [6]	18-26 years old female, N(I)=330; N(C)=331	-I: An individually tailored, online educational intervention on HPV vaccine-related knowledge, vaccination intention, and uptake among students -C: Online education from the CDC vaccine information statement -S: A Midwestern university	-42.9% of participants who received the first dose HPV vaccine received a second dose in each group.
Cates et al. 2011 [12]	9-13 years old female, N(I)=4 NC counties including Richmond, Harnett, Robeson and Cumberland; N(C)=9 NC counties	-I: Provided HPV vaccine promotion information through posters, brochure, websites, news releases and doctor's recommendations among parents -C: no intervention -S: Health care provider's offices and community including pharmacies, salons and grocery stores	-Cumulative HPV vaccination rates by age 9-13 from immunization registry system: -I (Richmond): 7.1% -I (Harnett): 6.8% -I (Robeson): 3.2% -I (Cumberland): 1.9% -C: 5%
DiClemente et al. 2015 [13]	14-18 years old African-American female, N(I)=108; N(C)=108	-I: Innovative culturally tailored, computer-delivered media-based intervention (Girls OnGuard) to improve HPV knowledge, vaccine motivation and behavioral skills among adolescents -C: No intervention -S: Family planning and sexual transmitted infection public health clinics in metropolitan Atlanta	-6% (6/108) received doses 2 and 3 in the intervention group; 2% (2/108) received doses 2 and 3 in the control group; data from medical records
Gerend et al. 2012[14]	18-26 years old female, N (I1)=250; N (I2)=243;	-I1: Educational video with gain-framed information for HPV vaccination and HPV infection	-Series initiation rates by self-report: -I1: 5% -I2: 6%

	N (C)=246	-I2: Educational video with loss-framed information for HPV vaccination and HPV infection -C: Educational video with no framed information for HPV vaccination and HPV infection -S: A large southeastern university in the U.S.	-C: 7%
Groom et al. 2017 [49]	11-18 years old female and male	-Pre- and post-intervention: Education session combining information on HPV infection, parental communication strategies, and facility-specific coverage data among adolescents among health care team members such as administrative, medical assistants, nurses, medical doctors -S: Primary care facilities within the Kaiser Permanente Northwest health care system	-Series initiation rate for female: increased by 1% -Series initiation rate for male: increased by 3%
Hohmeier et al. 2016[50]	9-26 years old female and male, 21 questionnaire respondents	-Pre- and post-intervention: A pharmacist-led, multimodal educational intervention approach -S: A community pharmacy setting	-Series initiation rate: increased to 48%
Hopfer 2012[15]	18-26 years old female, N=404	-I1: A narrative video with peer narrative intervention -I2: A narrative video with medical expert narrative intervention -I3: A narrative video with combined peer and medical expert narrative intervention	-Series initiation rates by self-report: -I1: 18% -I2: 6% -I3: 22% -C: 12%

		-C: No intervention -S: A university health center	
Jiménez-Quiñones et al. 2017 [51]	18-26 years old female and male, N=79	-Pre- and post-intervention: pharmacist conducted educational program that educational materials and counseling regarding HPV vaccination were provided to patients -S: A pharmacy in Farmacia San José, Lares, PR	-4 patients received an HPV vaccine dose after the intervention
Obulaney et al. 2016 [16]	9-18 years old female, N=41	-Pre- and post-intervention: Nurse practitioner-led language-appropriate cervical cancer prevention educational session among mothers and daughters -S: A low-cost, faith-based clinic	-HPV vaccine rate increased from 5.4% to 18% after the intervention
Parra-Medina et al. 2015 [17]	11-17 years old Hispanic female, N(I)=257, N(C)=115	-I: Entre Madre e Hija (EMH): A culturally relevant cervical cancer prevention program and HPV vaccine educational brochure -C: HPV vaccine educational brochure -S: Community resource centers	-84% of participants in both I and C groups initiated HPV vaccination. Series completion rates among those who received HPV vaccine dose 1: -I: 72.2% -C: 42.5%
Pierre Joseph et al. 2016 [18]	11-15 years old Haitian American and African American female N(I)=100; N(C)=100	-I: A client-centered behavioral health education curriculum among mothers -C: Low-literacy, standard-practice HPV vaccine information sheet -S: Primary care practices of a large urban hospital	-Series completion rates from EHR: -I: 10% -C: 7%

Rickert et al. 2015 [52]	11-15 years old female and male, N=445	-Pre- and post-intervention: A parent health education with rhetorical or non- rhetorical question and one-sided or two-sided message among parents -S: Teen Health Center	-151 participants received their first dose (34%)
Sanderson et al. 2017 [38]	9-18 years old African American and Hispanic female and male, N(I)=150 families (194 children); N(C)=119 families (167 children)	-I: Provider/staff training sessions and provision of patient education materials -C: no intervention -S: 4 Safety-net pediatric clinics	-Series completion rates from medical records: -I: 12.4% -C: 18.0%
Staras et al. 2014[53]	11-17 years old female and male, N(I1)=2,839; N(C1)=2,824; N(I2)=1,774; N(C2)=3,889; N(I3)=886; N(C3)=1,936	-I1: Postcard campaign: address the gender diversity in vaccine series initiation and differential parent concerns. It was used to urge parents to discuss vaccination with the health care's providers. -I2: In-clinic health information technology (HIT) system: to verify adolescent's vaccination history and indicate interest in learning the vaccine. It reminded providers if the adolescents agreed to the vaccination. -I3: Postcard campaign and in-clinic HIT system C1-C3: Usual care -S: Primary care clinics in North Central Florida	-Series initiation rates among girls: -I1=5.5%; C1=3.6% -I2=6.0%; C2=4.8% -I3=7.5%; C3=3.1% -Series initiation rates among boys: -I1=5.7%; C1=5.4% -I2=7.0%; C2=4.8% -I3=7.2%; C3=4.7%

Vanderpool et al. 2013 [19]	Mean age of 22 years old Appalachian female, N(I)=178; N(C)=166	-I: Educational DVD for HPV vaccination -C: Standard care -S: Community	-Series completion rate: -I=43.3% -C=31.9%
Wedel et al. 2016 [20]	18-26 years old military female, N=103	-Pre- and post-intervention: patient education and provider recommendation program -S: A medical facility in southern California	-Series initiation rate: increased from 55% to 91%
Provider assessment and feedback (N=1)			
Perkins et al. 2015 [57]	11-12 years old female and male, N(I)=4093; N(C)=9025	-I: Provider-focused intervention that included individualized feedback that showed providers' performance compared to others in immunization rates, and quality improvement incentives when demonstrating improvements in immunization rates -C: No intervention -S: Federally qualified community health centers	-Completion of next needed dose of HPV vaccine among females: increased from 44% to 56% in the intervention group and from 40% to 44% in the control group - Completion of next needed dose of HPV vaccine among males: increased from 1% to 59% in the intervention group and from 13% to 41% in the control group
Provider reminders (N=2)			
Soon et al. 2017 [21]	18-26 years old female, N=241	-Pre- and post-intervention: the electronic medical record prompt on HPV vaccine -S: An outpatient clinic	-HPV vaccine uptake: increased from 1.2% to 26.5% after the intervention
Szilagyi et al. 2015 [59]	11-17 years old female and male, N(I)= 11 clinics (5 GR-PBRN practices	-I: In the first strategy, an electronic health record appeared on the providers' computer screen to indicate the specific immunizations that adolescents were recommended to receive (EHR-Prompt). In	-Series completion rates among females in GR-PBRN clinics remained unchanged at 51%in the intervention group, but increased

	and 6 CORNET practices), N(C)= 11 clinics (5 GR-PBRN practices and 6 CORNET practices)	the second, a nurse- or staff-initiated provider prompt appeared on the providers' reminder sheet (Staff-Prompt) -C: Standard-of-care without prompts -S: Pediatric or family medicine clinics in the Practice-based research networks (PBRN)	from 51% to 53% in the control group[a] -Series completion rates among females in CORNET clinics increased from 48% to 50% in the intervention group, but decreased from 44% to 42% in the control group[b]
Reducing out-of-pocket costs (N=3)			
Casey et al. 2013 [22]	18-26 years old Appalachian female, N=495	- Pre- and post-intervention: Free voucher to receive three doses of HPV vaccine series -S: (1) Health clinics for primary care and women's health service; (2) Community college	-Series initiation rate: increased to 25.9%
Moore et al. 2010 [23]	18-24 years old female, N=209	-Pre- and post-intervention: Free voucher to receive three doses of HPV vaccine series -S: A university health clinic	-Series completion rate: increased to 28.2%
Vanderpool et al. 2011 [24]	18-26 years old Appalachian female, N=247	-Pre- and post-intervention: Free voucher to receive three doses of HPV vaccine series -S: Health clinics in rural counties of Southeastern, Kentucky	-Series initiation rate: increased to 44.9%
Vaccination program in school (N=4)			
Daley et al. 2014 [25]	6th to 8th grade female N(I)=7 schools (median number of	-I: Three-day school-located adolescent vaccination program. The vaccine program is in partnership with a local health department	-Percentages of receiving one or more doses among students needing vaccine (6th grade): 34% in the

	students =289); N(C)=7 schools (median number of students=350)	-C: No intervention -S: Vaccination clinics at seven Denver public schools	intervention group and 18% in the control group - Percentages of receiving one or more doses among students needing vaccine (7th and 8th grade): 20% in the intervention group and 7% in the control group
Eldred et al. 2015 [61]	Middle school female and male, N=184	-Pre- and post-intervention: Medical student-driven "vaccine blitzes" to vaccinate all consenting students. Vaccines were given by a team of medical students, public health students and school-based health center staff - S: School-based health center	-Series initiation rate among girls: increased from 7% to 41% -Series initiation rate among boys: increased from 7% to 31%
Navarrete et al. 2014 [26]	≥19 years old female, N=89	-Pre- and post-intervention: a pharmacist-operated HPV vaccine program utilizing patient assistance program (PAP). The pharmacist administered the HPV vaccine for the uninsured and underinsured student population. -S: University of Texas at El Paso University Student Health Clinic Pharmacy	-Series completion rate: increased to 48.3%
Stubbs et al. 2014 [27]	Middle school female, N(I)=6 schools; N(C)=15 schools	-I: Hosted a 4-day school-located HPV vaccination clinic which provided free HPV vaccine to the study. The vaccine program is in partnership with a local health department.	-Series initiation rates: 6% in the intervention group and 1% in the control group

		-C: Students could receive the HPV vaccine at the intervention school clinics -S: Middle schools in Guilford county, NC	
Vaccination requirements for school attendance (N=3)			
Moss et al. 2016 [28]	13-17 years old female, N=47,742	-I: State school entry requirements for adolescent vaccination (Virginia and the District of Columbia) -C: No state school entry requirements for adolescent vaccination	-Series initiation rates by the analysis of 2008-2012 National Immunization Survey-Teen: 47.7% in the intervention group and 47.3% in the control group
Perkins et al. 2016 [29]	13-17 years old female, N(I1)=1,649; N(I2)=12,579; N(C)=33,617	-I1: School-entry mandates for HPV vaccination (Virginia and the District of Columbia) -I2: Mandates of education to parents or provision of education within school curricula (LA, MI, CO, IN, IA, IL, NJ, NC, TX, WA) -C: No mandates	-Series completion rates by the analysis of the 2009 – 2013 National Immunization Survey-Teen -I1: increased from 28% to 39% -I2: increased from 29% to 37% -C: increased from 29% to 38%
Potter et al, 2014 [30]	6th grade female, N=264,789	-Pre and post-intervention: initiation of the HPV vaccine series required for 6th grade	-Series initiation rate (analysis of the Michigan Care Improvement Registry): increased less than 5% after the intervention
Intervention combination: Patient reminder and recall system+ patient education (N=7)			
Aragones et al. 2015 [39]	9-17 years old Mexican-American male and female, N(I)=45; N(C)=24	-I: Parental education and a text messaging reminder intervention -C: education onsite only -S: A non-clinical, trusted community setting	-Series completion rates among those who received the first dose by self-reported: -I: 88% -C: 40%

Cassidy et al. 2014 [31]	11-12 years old female, N(I)=24; N(C)=29	-I: Evidence-based educational brochure and reminder system - C: no intervention - S: Private pediatric practice in an urban location	-Series completion rates by self-reported: -I: 62.5% -C: 6.9%
Paskett et al. 2016 [32]	9-17 years old Appalachian female: N(I)=174, N(C)=163	-I: HPV education materials using examination room poster, brochures and tabletop + a magnet reminder for the 2nd and 3rd HPV vaccine shot -C: No intervention -S: Clinics in Appalachia Ohio	Series initiation rates from medical records: -I: 13.1% -C: 6.5%
Patel et al. 2012 [33]	18-26 years old female: N= 256	-I: HPV education with a mailed reminder -C: standard care -S: A university health service gynecology clinic	Series initiation rates from medical records: -I: 5.5% -C: did not differ by intervention group
Richman et al. 2016 [62]	18-26 years old female and male, N(I)=129; N(C)=133	-I: Text/ E-mail appointment reminders and education message -C: standard of care -S: A University health center in North Carolina	-Series completion rates from student health records: -I: 34% -C: 32%
Tiro et al. 2015 [63]	11-18 years old female and male, N(I)=410; N(C)=404	-I: HPV vaccine-specific brochure and reminder calls; -C: General vaccine brochure -S: 4 safety-net pediatric clinics	-Series completion rates from electronic health records: -I: 28.7% -C: 15.6%

Vanderpool et al. 2015 [64]	9th to 12th grade female and male, N=447	-Pre and post-intervention: A school-based HPV vaccine program. The vaccine program is in partnership with a local health department. The intervention included HPV educational materials and telephone reminder calls -S: School health centers in rural south-central Kentucky	-Series completion rate: increased from 14% to 45%
Intervention combination: Patient reminder and recall system+ provider assessment and feedback (N=2)			
Mazzoni et al. 2016 [34]	15-26 years old female, N=4869	-Pre- and post-intervention: Reminder/ recall program, give provider feedback on immunization and staff education -S: Obstetrics and gynecology clinics at a public integrated health-care system	Series initiation rate: increased from 7.1% to 23.7%
McLean et al. 2017 [65]	11-17 years old female and male, N(I)=16,401; N(C)=8,617	-I: Provider and staff education, quarterly feedback to providers and patient reminder and recall notices -C: No intervention -S: Pediatrics and family practices in Marshfield Clinic Health System	-Series completion rates among 11-12 adolescents: -I: increased from 32.0% to 52.7% -C: increased from 31.6% to 52.3% -Series completion rates among 13-17 adolescents: -I: increased from 59.4% to 71.9% -C: increased from 55.5% to 66.9%
Intervention combination: Patient education+ provider assessment and feedback (N=2)			
Jacobs-Wingo et al. 2017 [66]	13-17 years old American Indian female and male, N=6,239 (14 facilities)	- Pre- and post-intervention: Analyzing and providing feedback on facility vaccine coverage data + patient and provider education	Series completion rate from facility's EHR: increased from 20% to 42%

		- S: Indian Health Service, tribally-operated, and urban Indian (I/T/U) healthcare facilities	
Zimmerman et al. 2017 [67]	11-13 years old female and male, N(I)=4942; N(C)=5919	- I: Educated patients about the importance of immunization and the availability of vaccines, and provided assessment and feedback on immunization rates while motivating physicians through an office immunization champion -C: No intervention -S: Primary care family medicine and pediatric practices in Pittsburgh and Southwestern Pennsylvania	-Series completion rates from EHR -I: from 31.3% to 44.1% -C: from 37.3% to 50.0%
Intervention combination: Provider education + provider reminder+ provider assessment and feedback (N=1)			
Fiks et al. 2013 [35]	11-17 years old female, N (I1)=5,680; N (I2)=5,557; N (I3)=5,561; N (C)=5,688	-I1(Family-focused intervention): Automated educational reminder calls for patients -I2(Clinician-focused intervention): EHR-based clinician-focused vaccine alerts+ automated educational reminder calls for patients+ performance feedback reports for vaccine delivery -I3(Combined intervention): I1 and I2 combined intervention -C: Standard of practice -S: The Children's hospital of Philadelphia Pediatric	Series completion rates: -I1: 73% -I2: 67% -I3: 76% -C: 63%
Intervention combination: Provider assessment and feedback + standing orders + immunization information systems (N=1)			

Moss et al. 2012 [36]	12-17 years old female, N=17 clinics	-Pre- and post-intervention: a webinar that reviewed provider-based changes and weekly follow-up E-mails, provided incentives and identified the champion on immunization practices. Clinic staffs learned to use standing orders and the North Carolina Immunization Registry to improve immunization rates - S: Federally qualified health centers	-Series completion rate from NC immunization registry: increased from 21% to 22%
Intervention combination: Provider reminders + standing orders + immunization information systems + vaccination program in school (N=1)			
Farmar et al. 2016 [68]	13-17 years old female and male, N=11463	I: Clinic staffs checked vaccine registry for recommended vaccines at every visit. Routine use of a vaccine registry and standing order for the vaccination to be administered to the patient. Vaccination drives at school health centers were offered. -C: compared with national HPV vaccine coverage -S: Denver Health: an integrated urban safety net health system	-Series completion rates among girls from vaccine registry: 66.0% in the intervention group versus 37.6% nationally -Series completion rates among boys from vaccine registry: 52.5% in the intervention group versus 13.9% nationally

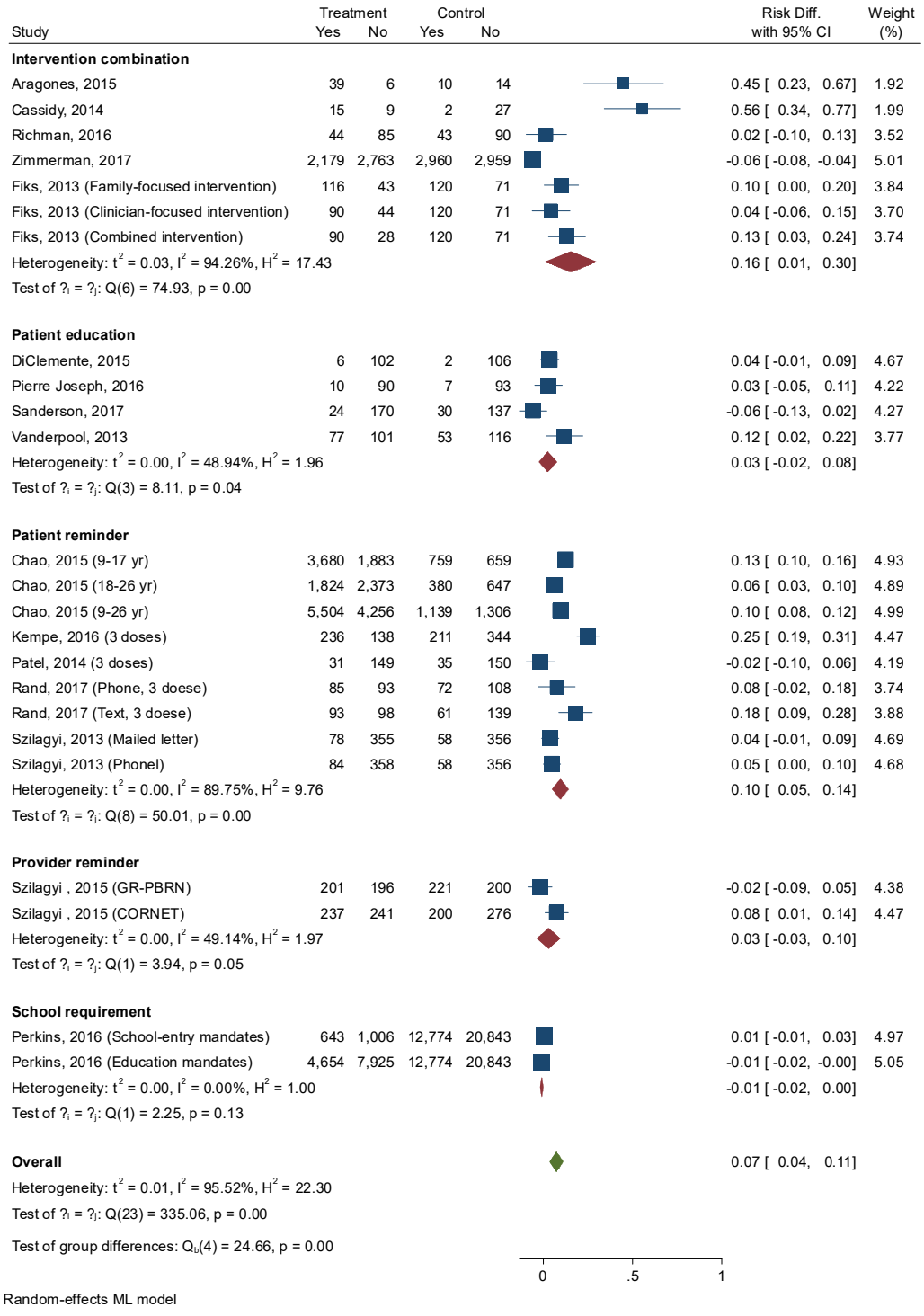
SES: Social economic status; I: Intervention; C: Control; CDC: Centers for Disease Control and Prevention; NC: North Carolina; EHR: Electronic health record; PR: Puerto Rico

Table 3. Study characteristics for the included economic studies

Author/year	Intervention types	Evidence relevant to costs in the study
Patient reminder and recall systems		
Bar-Shain et al. 2015 [46]	Immunization message reminder including automated voice, texts and postcards	-5,965 text and phone messages sent; <$.10 per automated message for e-mail, text, and phone messages -1,129 postcards sent; $1.50 per postcard
Suh et al. 2012 [42]	Consisted of up to 2 letters separated by 2 autodialed telephone calls	-Total operating costs in four implemented practices=$1,119+$1,245+$1,349+$1,087=$4,800 -Total personnel costs in four implemented practices=$589+$420+$622+$458=$2,089 -Total supply costs in four implemented practices=$530 +$825+$727+$629=$2,711
Szilagyi et al. 2013[37]	Included reminder letters and telephone	-The cost for the mailed reminder letter was $18.78 per adolescent - The cost for the telephone reminder was $16.68 per adolescent -The cost for the mailed reminder letter was $463.99 per additional adolescent fully vaccinated -The cost for the telephone reminder was $714.95 per additional adolescent fully vaccinated
Patient education		
Karanth et al. [54]	i-Pad based tailored interactive multimedia intervention (TIMI) or print based (Photonovella)	-TIMI: Total direct cost including personnel and material cost=$80.64 per participant; Overhead cost=$24.19 per participant; Participant time cost=$2.99 per participant -Photonovella: Total direct cost including personnel and material cost=$65.49 per participant; Overhead cost=$19.65 per participant; Participant time cost=$2.36 per participant
Vaccination program in school		
Daley et al. 2014 [25]	School-located vaccination program	-A total of 1,505 vaccines administered; the estimated program administration costs were $23.98 per vaccine administered
Stubbs et al. 2014 [27]	School-located HPV vaccination clinics	-Total costs were 36% of the $376,104 budget= $135,398
Provider education+ provider reminder+ provider assessment and feedback		
Fiks et al. 2013 [35]	EHR-based vaccine alerts+ automated educational	-Family-focused intervention: Total costs for administering HPV vaccine 1 to 3 were $2,455

	reminder calls for patients+ performance feedback reports for vaccine delivery	-Clinician-focused intervention: Total costs for administering HPV vaccine 1 to 3 were $7,488 -Combined intervention: Total costs for administering HPV vaccine 1 to 3 were $9,946

Figure 6. Forest plot for the outcome effect of HPV vaccine promotion interventions on HPV series completion rate



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JOURNAL ARTICLE-2

A cost-effectiveness analysis of HPV vaccine promotion interventions

American Journal of Preventive Medicine

Background

Human papillomavirus (HPV) vaccines have proven capable of substantially reducing the risk of cervical cancer. However, HPV vaccine coverage in the U.S. has been relatively low. From the latest data of HPV vaccine coverage in the U.S., 53.7% of girls aged 13-17 years old were up to date with HPV vaccine series in 2018.[1] This is significantly below the CDC's Healthy People target of 80% coverage by 2020 . By comparison to rates in other developed countries, the HPV vaccine coverage rate in Australia among females at age 15 reached to 85% in 2017.[2] The HPV vaccine coverage in the United Kingdom among females aged 12-13 years was 90% in 2018.[3] Given that the coverage rate is sub-optimal in the U.S., improving HPV vaccine coverage is a consequential public health issue. Implementing interventions designed to promote the HPV vaccine is the main approach to increasing HPV vaccine coverage in the U.S. The Community Preventive Services Task Force (the Community Guide) identified a number of strategies for increasing vaccine coverage. Strategies include home visits, school requirements, patient reminder and recall system, provider assessment and feedback, provider reminders, standing orders, reducing client out-of-pocket costs, immunization information systems, school-based vaccine programs, community-based intervention combination, and health care system-based interventions.[4] However, the cost-effectiveness of implementing such interventions remains unknown. Resources required of implementing interventions varied and the cost-effectiveness is an

important consideration. The aim of this study was to assess the cost-effectiveness of interventions designed to increase HPV vaccine coverage in the U.S.

Methods

We assessed the cost-effectiveness of several U.S. HPV vaccine promotion interventions versus current practice. The data for both cost and effectiveness were derived from relevant published literature. The HPV vaccine is recommended for individuals at ages 11-12; the vaccine can be given as early as age 9.[5] Our focus for included literature is on the age of 9 to 12 years old. In our previous systematic review study, we have identified interventions used to improve the HPV vaccine coverage, including patient reminder and recall system, patient education, provider assessment and feedback, provider reminders, standing orders, reducing client out-of-pocket costs, immunization information systems, school-based vaccine programs, school requirements, community-based intervention combination, and health care system-based interventions. Interventions if either cost or effectiveness are not available in the literature were excluded. After identifying evidence of intervention costs and effectiveness, we included patient reminder and recall system, patient education, provider reminders, reducing patient out-of-pocket costs, school-based vaccine programs, and community-based intervention combinations in the evaluation. The primary outcome measures for this study were incremental cost-effectiveness ratios (ICERs), which were computed by the following equation.

$$\text{ICER} = \frac{Cost_{intervention} - Co \quad no\ intervention}{HPV\ vaccine\ series\ completion\ rate_{intervention} - HPV\ vaccine\ series\ completion\ rate_{no\ intervention}}$$

ICERs represented the cost per additional intervention individuals that completed the HPV vaccine series, compared with current practice. A secondary analysis was conducted in which the effectiveness of ICERs was measured by the percentage

increase of receiving at least one HPV vaccine dose of interventions. The secondary analysis ICER was computed by the following equation.

$$\text{ICER} = \frac{Cost_{intervention} - Cost_{no\ intervention}}{Receiving\ at\ least\ one\ HPV\ vaccine\ dose_{intervention} - Receivin\quad at\ least\ one\ HPV\ vaccine\ dose_{no\ intervention}}$$

ICERs of secondary analysis represented the cost per additional intervention individual that received at least one HPV vaccine dose. To address the issue of the parameter uncertainty, sensitivity analysis was performed. We varied the cost and effectiveness for the HPV vaccine promotion intervention with plausible estimates derived from published literature.

Effectiveness estimation

The HPV vaccine series completion rate of the intervention was computed by the percentage change of completing the HPV vaccine series between intervention and control groups. The outcome of receiving at least one HPV vaccine dose was measured by the percentage change of receiving at least one HPV vaccine dose between intervention and control groups. The HPV vaccine completion rate for the patient reminder and recall system was derived from a study of Kaiser Permanente Southern California Health Plan female members aged 9-26 years old. They found the HPV vaccine series completion rates were 56% and 46% in the intervention and control groups, respectively.[6] Data for receiving at least one HPV vaccine dose was derived from a study in which text message reminders for the next needed HPV vaccine doses were sent to parents of adolescents aged 9 to 20 years old. Percentages of receiving at least one HPV vaccine dose were 52% and 35% in the intervention and control groups, respectively.[7]

We identified 16 studies that used patient education to increase HPV vaccine coverage. Only 4 studies among them reported the percentage change of HPV vaccine series completion rate between intervention and control groups.[8–11] Since 4 studies all

focused on a specific population (e.g. Appalachian or African American and Hispanic females), we applied a median change of 6% among studies in the base-case analysis (range of values: -6% to 25%). We found 10 patient education interventions that measured percentage changes for receiving at least one dose of HPV vaccine. Among them, 2 studies (including 10 intervention arms) were implemented in our age group. The remaining interventions were excluded because they were implemented in either an age group which was older than 12 years old or a specific population (e.g. African-American or Haitian American females). We applied a median change of 2% among studies in the base-case analysis (range of values: -3% to 4%).[12,13]

The HPV vaccine completion rate of provider reminder was estimated from a randomized controlled trial in which they assessed immunization rates on provider prompts at health care visits among 11-17 years old adolescents. They found HPV vaccine completion rates were 50% and 42% in the intervention and control groups, respectively[14]. Data on percentages receiving at least one dose HPV vaccine of provider reminders were not available in the literature. We used information published by the Community Guide that they reviewed interventions by using provider reminders to increase immunization rates (eg. influenza or pneumococcal). They concluded that an overall median increase of immunization rate for the provider reminder is 10%.[15]

We identified 3 studies that used interventions designed to reduce out-of-pocket costs to increase HPV vaccine coverage. In the 3 studies, outcomes of HPV vaccination rates were measured before and after the intervention among females older than 18 years old. We applied the result from Moore et al. study for the HPV vaccine completion rate since it was the only study that reported the completion rate. The study offered free 3-dose HPV vaccine for females aged 18 to 24 years old. After the intervention, about 28% of participants completed the series of HPV vaccination. [16]Data

on percentages receiving at least one dose HPV vaccine of the intervention were derived from a study in which an HPV vaccine voucher was offered to redeem the 3 dose HPV vaccine series without a charge among 247 Appalachian women. After the intervention, 45% of the study participants redeemed the coupon to receive the first dose of HPV vaccine.[17]

Information on the HPV vaccine completion rate of school-based vaccine programs was not available from the literature. Therefore, we used the alternative effectiveness measurement of HPV vaccine initiation rate in the analysis. Data on the HPV vaccine initiation rate were derived from a study of school-located HPV vaccination clinics for middle school girls. They found that HPV vaccine initiation rates were higher among intervention schools than control schools (6% vs. 1%).[18] Data on the percentage of receiving at least one dose of HPV vaccine were derived from a study that assessed the impact on a school-located adolescent vaccination program in Denver public schools. Sixteen Denver public schools were eligible to participate in the study and were randomly assigned as intervention (n=8) and control schools (n=8). Intervention schools conducted school-located vaccination programs among 6th to 8th-grade students; whereas control schools did not. The HPV vaccine initiation rate among students needing a vaccine was higher in the intervention schools than control schools (20% vs. 7%) among 7th and 8th-grade female students.[19]

The community-based intervention combination combined patient reminder and recall system and patient education. Data for effectiveness was derived from a randomized controlled trial that evaluated effects of a multicomponent intervention including HPV vaccine brochure and recalls among girls aged 11 to 18 years old attending the pediatric clinic. They found that patients in the intervention groups were more likely to receive all 3 doses after the intervention compared with the control group

(28% vs. 15%, respectively).[20] Data on the percentage of receiving at least one dose HPV vaccine were derived from a study in which they assessed the effect of the educational brochure and a reminder system on the HPV vaccine uptake rate among eligible 11 to 12 years old girls. HPV vaccine uptake rates in the intervention and control groups were 75% versus 24%[21].

We assumed the current practice strategy would include the provision of standard HPV vaccine information sheets to the target population. The effectiveness of current practice was computed by the percentage change of the HPV vaccine coverage in the control group during the study period. Data on the effectiveness of current practice was derived from a study of adolescents aged 11 to 17 years old. Individuals in the control group received standard of care. They found that HPV 3 doses vaccination rate was 51% at baseline and increased to 53% at the end of the study period in the control group.[14]

Cost estimation

Costs were measured as intervention costs per person. Costs of administering the HPV vaccine such as physician fees and vaccine costs were excluded since we focused on getting the eligible participants to the point of choosing to be vaccinated, and not the cost-effectiveness of the vaccine which has been confirmed in several previous studies. All costs were adjusted to 2018 USD using the Consumer Price Index from the U.S. Bureau of Labor Statistics [22].

Costs of patient reminder and recall systems were estimated from Szilagyi et al. study. They conducted a randomized controlled trial to evaluate a managed care-based patient reminder and recall system. The intervention costs were $23 and $21 per adolescent for mailed letters and telephone reminders, respectively. We applied the mean value in base-case analysis [23].

Costs of patient education were derived from a study of print-based photonovella and iPad-based tailored interactive multimedia interventions (TIMI) to promote the HPV vaccine ($73 vs. $90). Costs documented in the study included personnel, material, overhead and participant time cost for the intervention. We excluded overhead and participant time costs since those data were not available for other interventions.[24]

Costs for both the provider reminder and the community-based intervention combination were not available in the HPV vaccine promotion intervention literature. Their cost estimates were derived from reports published by the Community Guide that systematically reviewed studies on immunization promotion interventions (eg. influenza or pneumococcal). Cost ranges for the provider reminder and the community-based intervention combination were $2 to $54 and $16 to $250 per person, respectively. We applied the mid-points of ranges ($28 and $133 for provider reminder and community-based intervention combination, respectively) in the base-case analysis and addressed the uncertainty in the sensitivity analysis.[15,25]

The cost of school-based vaccine programs was derived from a school-located adolescent vaccination program study. They reported that the cost of administering the program per vaccine dose was $30 and a total of 1,505 vaccine doses were administered among 527 students who consented to participate in the intervention. We estimated the intervention cost was $85 per participant.[19]

The cost data for reducing patients' out-of-pocket costs were not available from the literature. We assumed the cost of implementing the intervention is the sum for providing 3-dose HPV vaccinations ($178/ per dose per participant)[26] plus the material and personnel cost for implementing the intervention ($41/ per participant)[27].

We estimated costs of current practice were $3 per person, which is based on the printing and office costs of HPV vaccine information sheets derived from a study of clinic-based media intervention to promote HPV vaccination. [24]

Results

Parameters of cost and effectiveness used in the base-case and sensitivity analysis were presented in Table 4. Intervention costs ranged from $22 per individual (patient reminder and recall system) to $575 per individual (reducing out-of-pocket costs). For the effectiveness of interventions, the increase in HPV vaccine completion rate ranged from 5% (school-based vaccine programs) to 28% (reducing out-of-pocket costs). For the percentage increase of receiving at least one dose HPV vaccine, effectiveness ranged from 2% (patient education) to 51% (community-based vaccination combinations). Under base-case analysis when intervention effectiveness was measured by the increase of HPV vaccine completion rate, the cost per additional individual completed HPV vaccine series for the patient reminder and recall system was $238 compared with current practice (Table 5). Interventions of provider reminder, patient education, and school-based vaccine programs were dominated by patient reminder and recall system since they have higher costs but lower effectiveness than patient reminder and recall system. The community-based intervention combination was extended dominance since its ICER is greater than that of the reducing out-of-pocket costs intervention. The ICER of reducing out-of-pocket costs is $3,072, compared with patient reminder and recall system.

In the secondary analysis when the intervention effectiveness was measured by the percentage increase of receiving at least one HPV vaccine dose, the cost per additional individual received at least one HPV vaccine for the patient reminder and recall system was $107, compared with current practice. Provider reminder, patient education and

school-based vaccine programs were dominated by the patient reminder and recall system. The ICER of the community-based intervention combinations was $326, compared with the patient reminder and recall system. Reducing out-of-pocket costs were dominated by the community-based intervention combinations which has a lower cost but yields a better outcome on the percentage of receiving at least one dose HPV vaccine.

Parameters for both cost and effectiveness for the HPV vaccine promotion intervention varied in the sensitivity analysis with plausible estimates derived from published literature. Results for the one-way sensitivity analysis shown in the tornado diagram in Figure 7. Overall, intervention effectiveness has a greater impact on the ICER than varying the cost estimates. We examined the "best-case (the lowest cost and the highest effectiveness)" and "worst-case (the highest cost and the lowest effectiveness)" scenarios in the multiple-way sensitivity analysis (Table 7). In the best-case scenario, the most cost-effective intervention remained the patient reminder and recall system. In the worst-case scenario, the most cost-effective was provider reminder. The ICER of the provider reminder was $933 when compared with current practice.

Discussion

In the U.S., HPV vaccine coverage is suboptimal. Various interventions have been designed to improve coverage. In our previous systematic review study, we have identified interventions used to improve the HPV vaccine coverage, including patient reminder and recall system, patient education, provider assessment and feedback, provider reminders, standing orders, reducing client out-of-pocket costs, immunization information systems, school-based vaccine programs, school requirements, community-based intervention combination, and health care system-based

interventions. The consideration of cost-effectiveness of these interventions are important. However, there is limiter evidence on the cost-effectiveness of HPV vaccine promotion interventions. To our knowledge, this is the first economic evaluation assessing a range of HPV vaccine promotion interventions in the US. It provides decision-makers evidence-based information and analysis of uncertainty about interventions aimed to improve HPV vaccine coverage.

We found that patient reminder and recall system was the most cost-effective intervention when the intervention effectiveness was measured as either the increase of HPV vaccine series completion rates or the percentage of patients receiving at least one dose of the HPV vaccine. The cost per additional individual that completed the HPV vaccine series and the cost per additional individual received at least one dose of HPV vaccine for the patient reminder and recall system were $238 and $107, respectively. Provider reminder interventions of, patient education and vaccination program in schools were dominated by the patient reminder and recall system, which is both more effective and less expensive. Patient reminder and recall system was one of the interventions recommended by the Community Guide in increasing vaccine coverage. The Guide concluded that patient reminder and recall systems can be implemented for a large number of patients and achieve vaccinations with relatively few economic resources.[28] The intervention designed to reduce patient out-of-pocket costs and community-based intervention combinations were more effective in increasing HPV vaccination rates than the patient reminder and recall system but substantially increased the intervention cost per individual. Decision-makers need to consider the cost structure, the applicability of interventions (e.g. different population or settings) and their willingness to pay for implementing the interventions to determine which intervention would be justified and feasible.

There are uncertainties of cost and effectiveness parameters that exist in our study since evidence regarding the cost-effectiveness of HPV vaccine promotion intervention was little. To evaluate our parameter estimates, we used literature focusing on other immunization promotion interventions to discuss similarities and differences in results (Table 8).[29,30] The effectiveness of HPV vaccine promotion interventions including patient reminder and recall system, provider reminder, interventions designed to reduce patient out-of-pocket costs and community-based intervention combinations were similar to interventions intended to increase other immunizations. Vaccination programs in schools aimed to promote HPV vaccine have lower effectiveness, compared with interventions intended to increase other immunization coverage. Evidence on HPV vaccine coverage rates increased by the vaccination program in schools was limited. More research is needed to determine intervention effectiveness of school-based programs. For the effectiveness of patient education, it is challenging to compare the effectiveness of the HPV vaccine and other immunizations due to inconsistent results. The Community Guide finds insufficient evidence to determine the effectiveness of patient education. In the Briss et al. systematic review, the effectiveness of patient education has a wide range, ranging from -4% to 29%. Patient education is the most common approach to increase HPV vaccine coverage. Since there are many different ways of implementing patient education, it is challenging to determine the effectiveness across a range of delivery methods (e.g., person-to-person interactions, clinic-based educations, and mass or small media). Future studies should develop a more detailed category system of patient education in order to better quantify the impact. For the intervention cost, patient reminder and recall system used to improve HPV vaccine cost more, compared with other immunizations. Identifying cost evidence in the literature is challenging since cost measurements reported in the literature were

not our outcome of interest. We identified 7 studies that reported intervention costs. Two of them reported intervention costs per participant were included in our analysis. The remaining reported different cost estimates (e.g. cost per reminder sent, cost per intervention practice and total cost of intervention) and we included in our analysis if it is feasible to convert their cost outcome by using study information. The cost of implementing interventions is important information for the intervention planner. More evidence on intervention cost is needed in the future.

There are several limitations to this study. Firstly, the percentage change of HPV vaccine series completion rates of patient education derived from studies that focused on specific populations (e.g., Appalachian or African American and Hispanic females). Interventions were implemented in groups that may not be representative of findings in the general population. We performed a subgroup analysis which included interventions implemented among the specific populations (Table 6). Interventions of patient reminder and recall system, patient education, intervention combinations and reducing out-of-pocket costs were included in the subgroup analysis. Intervention combinations was the most cost-effective when we focused on the specific population. More data is needed to understand CEA results of interventions implemented in the specific population. Data on both the percentage change of receiving at least one dose HPV vaccine of provider reminder and HPV vaccine completion rate for the school-based vaccine programs were not available in the literature. For the percentage change of receiving at least one dose HPV vaccine of provider reminder, we used results from the Community Guide reports. They synthesized evidence of interventions intended to increase other immunizations, rather than the HPV vaccine. For the HPV vaccine completion rate for the vaccination program in schools, we used the HPV vaccine initiation rate in the base-case analysis. The effectiveness of school-based vaccine

programs might be overestimated since visits are needed to complete the HPV vaccine series. The analysis should be updated when data become available on school-based programs. Secondly, the costs of both the provider reminder and community-based intervention combinations intended to increase HPV vaccine coverage were not available from the literature. We estimated the effectiveness of community-based interventions from the Community Guide which reviewed interventions intended to improve other vaccinations, such as influenza or pneumococcal vaccinations. Sensitivity analyses were performed to address uncertainties in the estimates. When we varied parameters with the lowest costs and highest effectiveness (best-case scenario), patient reminder and recall system remained the most cost-effective intervention. In the worst-case scenario, patient reminder and recall system was dominated by current practice. Provider reminder was the most cost-effective intervention under the worst-case scenario.

Conclusion

We assessed the cost-effectiveness of several U.S. HPV vaccine promotion interventions versus current practice. Interventions of patient reminder and recall system, patient education, provider reminders, reducing patient out-of-pocket costs, school-based vaccine programs, and community-based intervention combinations were included in the evaluation. We found that patient reminder and recall system is the most cost-effective HPV vaccine promotion interventions. The cost per additional individual completed HPV vaccine series (ICER) was $238. When the intervention effectiveness was measured as the percentage change of receiving at least one dose HPV vaccine, the ICER for the patient reminder and recall system was $107.

Table 4. Costs and effectiveness for HPV vaccine promotion interventions.

Intervention	Cost [a]	Cost range	Effectiveness (1) [b]	Effectiveness (2) [c]	Effectiveness range
Current practice	$3[21]	0~$6[21]	+2%[12]	+2%[12]	NA
Patient reminder and recall system	$22[20]	$2[25]~$33[d]	+10%[6]	+17%[7]	0[28]~+25%[29]
Patient education	$73[21]	$37[e]~$90[21]	+7%[8–11]	+2%[30]	0[27]~+25%[10]
Provider reminder	$29[13]	$8[13]~$62[13]	+8%[12]	+10%[13]	+8%[12]~+17%[27]
Vaccination programs in schools	$85[16]	$43[e]~$128[d]	+5%[15]	+13%[16]	+5%[15]~+41%[31]
Reducing out-of-pocket costs	$575[32]	$40[21]~$724[32,33]	+28% [34]	+45%[14]	+10%[27]~+45%[14]
Intervention combinations [f]	$133[22]	$63[22]~$313[22]	+13%[17]	+51%[18]	+2%[35]~+56%[18]

a: Measured as cost per participant of the intervention

b: Measured as the percentage change of the HPV series completion rate between intervention and control groups

c: Measured as the percentage change of receiving at least one HPV dose between intervention and control groups

d: Information were not available in the literature. We assumed the highest cost of the intervention is the base-case value times 1.5

e: Information were not available in the literature. We assumed the lowest cost of the intervention is the base-case value times 0.5

f: Intervention combined patient reminder and recall system and patient education

Table 5. Base-case results of CEA for the HPV vaccine promotion interventions

Strategy[a]	Cost	Incremental cost	Effectiveness	Incremental Effectiveness	ICER
Primary outcome: Effectiveness was measured as the percentage change for the HPV vaccine series completion rate between intervention and control groups					
Current practice	$3	-	+2%	-	-
Patient reminder and recall system	$22	$19	+10%	+8%	$238
Provider reminder	$29	$7	+8%	-2%	Dominated
Patient education	$73	$51	+7%	-3%	Dominated
Vaccination programs in schools	$85	$63	+5%	-5%	Dominated
Intervention combinations	$133	$111	+13%	+3%	Extended dominance
Reducing out-of-pocket costs	$575	$553	+28%	+18%	$3,072
Secondary outcome: Effectiveness was measured as the percentage change for receiving at least one HPV vaccine dose between intervention and control groups					
Current practice	$3	-	+2%	-	-
Patient reminder and recall system	$22	$16	+17%	+15%	$107
Provider reminder	$29	$32	+10%	-7%	Dominated
Patient education	$73	$51	+2%	-15%	Dominated
Vaccination programs in schools	$85	$63	+13%	-4%	Dominated
Intervention combinations	$133	$111	+51%	+34%	$326
Reducing out-of-pocket costs	$575	$442	+45%	-6%	Dominated

a: Interventions were order from highest to lowest costs

Table 6. CEA for the HPV vaccine promotion intervention among specific populations

Strategy[a]	Cost	Incremental cost	Effectiveness	Incremental Effectiveness	ICER
Current practice	$3[24]	-	+2%[14]	-	-
Patient reminder and recall system	$22[23]	$19	+5%[23]	+3%	Extended dominance
Patient education	$73[24]	$55	+7%[8–11]	+2%	Extended dominance
Intervention combinations	$133[25]	$130	+25%[37]	+23%	$565
Reducing out-of-pocket costs	$575[34]	$442	+36%[17]	+11%	$4018

Figure 7. Tornado diagram of the one-way sensitivity analysis: comparisons between HPV vaccine promotion interventions and current practice

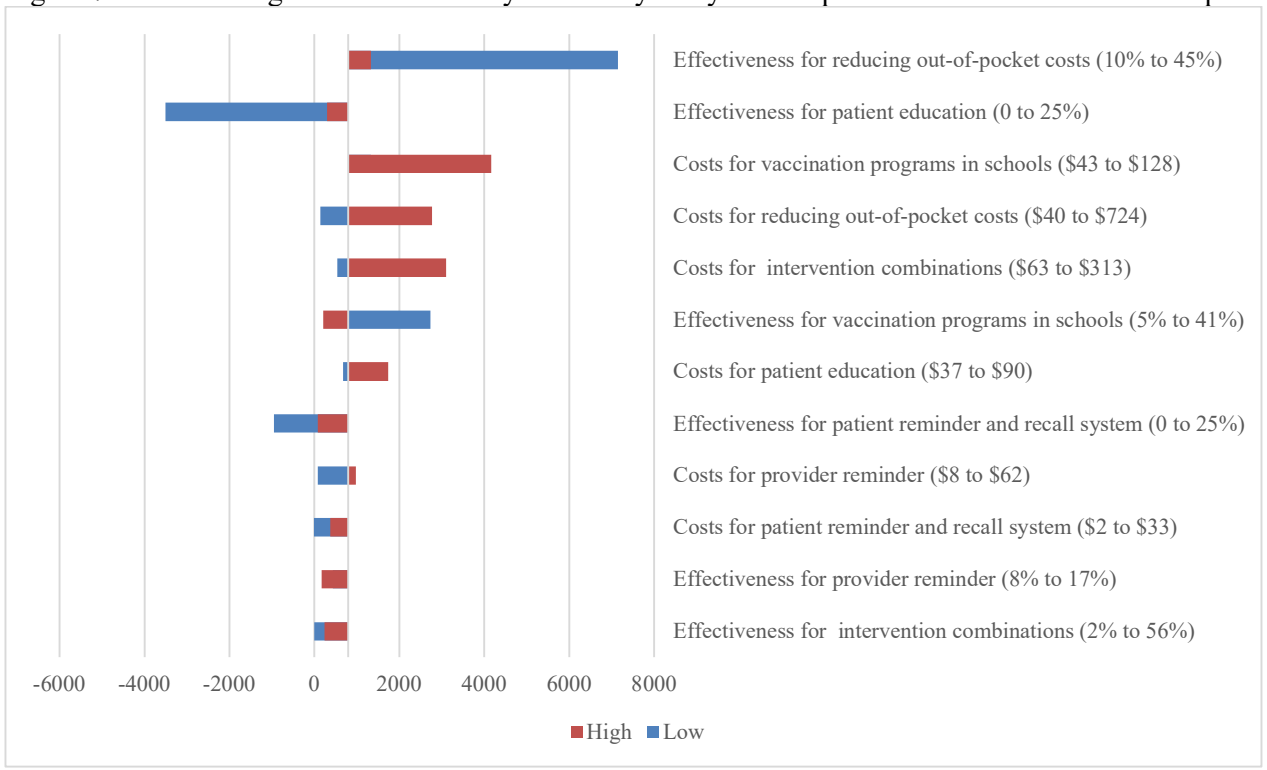

Table 7. Results of the multiple-way sensitivity analysis for HPV vaccine promotion interventions in the CEA

Strategy[a]	Cost	Incremental cost	Effectiveness	Incremental Effectiveness	ICER
The best-case scenario: the lowest costs and highest effectiveness for HPV vaccine promotion interventions					
Current practice	0	-	+2%	-	-
Patient reminder and recall system	$2	$2	+25%	+23%	$9
Provider reminder	$8	$6	+17%	-8%	Dominated
Patient education	$37	$35	+25%	0	Dominated
Reducing out-of-pocket costs	$40	$38	+45%	+20%	$190
Vaccination programs in schools	$43	$3	+41%	-4%	Dominated
Intervention combination	$63	$23	+56%	+11%	$209
The worst-case scenario: the highest costs and lowest effectiveness for HPV vaccine promotion interventions					
Current practice	$6	-	+2%	-	-
Patient reminder and recall system	$33	$27	0	-2%	Dominated
Provider reminder	$62	$56	+8%	+6%	$933
Patient education	$90	$28	0	-8%	Dominated
Vaccination programs in schools	$128	$66	+5%	-3%	Dominated
Intervention combination	$313	$251	+2%	-6%	Dominated
Reducing out-of-pocket costs	$724	$662	+10%	+2%	$33,100

a: Interventions were order from highest to lowest costs

Table 8. Comparisons with the cost and effectiveness results with literature reviewing immunization promotion interventions

Strategy	Effectiveness		Cost	
	The Community Guide	Briss et al. (2000)	The Community Guide[a]	Briss et al. (2000)
Patient reminder and recall system	Vaccination rates increased by a median of 11 percentage points (median increase of 6 and 12 percentage points when used alone and with additional components, respectively)	Vaccination rates increased by a median of 12 percentage points (median increase of 8 and 16 percentage points when used alone and with additional components, respectively)	Median cost per person per year of $2.43	$0.65 to $5.75 per child
Patient education	Insufficient evidence to determine the effectiveness	Percentage point changes in vaccination coverage ranged from -4% to 29%[b]	No economic evidence	No evidence on cost per person reported
Provider reminder	Vaccination rates increased by a median of 10 percentage points (median increase of 12 and 9 percentage points when used alone and with additional components, respectively)	Vaccination rates increased by a median of 17 percentage points (median increase of 17 and 14 percentage points when used alone and with additional components, respectively)	Median cost per person per year of $7.98	No evidence on cost per person reported
Vaccination programs in schools	Vaccination rates increased by a median of 41 percentage points	No evidence on percentage point change on vaccination rates reported	No economic evidence	No economic evidence

Reducing out-of-pocket costs	Vaccination rates increased by a median of 22 percentage points (median increase of 28 and 20 percentage points when used alone and with additional components, respectively)	Vaccination rates increased by a median of 15 percentage points (median increase of 10 and 16 percentage points when used alone and with additional components, respectively)	Median cost per person per year of $50.74	No evidence on cost per person reported
Community-based intervention combinations [c]	Vaccination rates increased by a median of 16 percentage points	No evidence reported	Median cost per person per year of $63.08	No evidence reported

a: costs were updated to year of 2018

b: data were derived from multiple components interventions which included patient education

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JOURNAL ARTICLE-3

A Cost-utility analysis of implementing the HPV vaccine promotion interventions of cervical cancer

Vaccine

Background

Human papillomavirus (HPV) vaccines have been proven capable of substantially reducing the risk of cervical cancer. Between 2012 and 2016, the average annual number of diagnosed HPV-associated cervical cancers in the U.S. was 12,015. Of these cases, an estimated 9,700 (81%) were attributable to the cancer types targeted by the 9 valent HPV vaccine.[1] According to an economic evaluation of the HPV vaccine, researchers concluded that HPV vaccination is cost-effective for cancer prevention in comparison to the current standard prevention strategy.[2] Regrettably, HPV vaccine coverage in the U.S. has remained relatively low. According to recent data estimating the vaccine's coverage, the up-to-date coverage in 2017 was only 48.6% among adolescents aged 13-17 years.[3] This rate of coverage is far below the CDC's Healthy People target of 80% coverage by 2020. Intervention strategies designed to promote the HPV vaccine are the main approach to increasing its overall coverage. However, the cost-effectiveness of implementing HPV vaccine promotion interventions has remained unknown. In this study, we conducted an economic evaluation to assess interventions designed to increase HPV vaccine coverage in the United States.

Methods

A CUA was conducted which compared the following HPV vaccine promotion interventions versus current practice: 1) patient reminder and recall system, 2) patient education, 3) provider reminder, 4) vaccination program in schools, 5) reducing out-of-pocket costs and 6) intervention combination (patient reminder and recall system and patient education). Current practice was defined that no particular intervention is implemented to improve the vaccination rate. Consolidated health economic evaluation reporting standards (CHEERS) was used as a guideline for conducting the health economic study. The CHEERS checklist was presented in table 9. The target population of this study was all adolescent girls in the U.S. Societal perspectives were applied in the study. A Markov model was used to simulate the natural history of cervical cancer. Markov model has been proven to be able to represent the natural history of cervical cancer appropriately and adequately address the decision problem of the HPV vaccination program.[4,5] We followed a cohort of women starting at age 12 until all of them died. The catch-up HPV vaccine through age 26 was added to the model. Health states and allowed transitions between health states are presented in Figure 8. The health outcome modeled in the study was quality-adjusted life-years (QALYs). All costs were then updated to 2018 USD using the Medical Care Component of the Consumer Price Index. [6] We followed the recommendation of the Panel on Cost-Effectiveness in Health and Medicine for applying 3% discount rates to both costs and utilities. [7] The outcome of the study was ICER, which was computed based on the following formula:

$$\text{ICER} = \frac{Cost_{intervention} - Co\ \ no\ intervention}{QALY_{intervention} - QALY_{no\ intervention}}$$

The half-cycle correction was applied for the model adjustment. We performed the sensitivity analysis to address uncertainties. In the probabilistic sensitivity analysis (PSA), main input parameters were changed and ran 1000 Monte-Carlo simulations with sampling from defined distributions. Gamma distributions were applied to the incidence rates of HPV infections and cervical cancer treatment costs. The standard error of the parameters was defined as 10% of the point estimates. Beta distribution was applied to the utility weights of the cancer stages and the standard error of the parameters was defined as 25% of the point estimates.[8] Models were analyzed using TreeAge Pro decision frameworks (TreeAge Software, 2018).

In Figure 8, the node below the boxed intervention options represents the vaccination decision following the implementation of an intervention. A natural history of cervical cancer thereafter is simulated using a Markov model. Each year, women are at risk of developing high-risk types of HPV infection, low-grade or high-grade squamous intraepithelial lesions (LSIL and HSIL), or cervical cancer. Once a person is infected with HPV, the conditions could regress to negative HPV infection or progress to either LSIL or HSIL. Females can develop cervical cancer from high-grade SIL and progress to invasive local cervical cancer, regional invasive cervical cancer, and distant invasive cervical cancer. In this analysis, cancer cases are treated if detected. After successful treatment, those cases are moved to the cancer survivors compartment, and regression from cancer to normal is not allowed [5,9].

Model parameters

Model parameters were derived from the published literature (Table 10). We used U.S. data for our parameters as much as possible to better reflect the realities. Each cycle is assumed to be one year. Death rates for females without cervical cancer were

obtained from Vital Statistics data.[10] Summaries of data sources for parameters used in the base-case analysis are described below, including HPV vaccine intervention costs and effectiveness, HPV vaccine cost and coverage, HPV infections, LSIL and HSIL, cervical cancer, cancer costs, and utilities.

HPV vaccine intervention costs and effectiveness

Costs and effectiveness of HPV vaccine promotion intervention were measured as intervention costs per person and HPV vaccine series completion rates, respectively. The data for both cost and effectiveness were derived from relevant published literature. Rationales on intervention cost and effectiveness data selections have been described in the aim 2 method section.

HPV vaccine cost and coverage

The cost for the HPV vaccine per dose is $203, which is the average of the public and private costs [11]. Cost (2018 year) for the administration fee and supply and patient time are assumed $8.65 and $34.60, respectively [12]. The cost for the HPV vaccine per 3 doses is assumed as $739 in the base-case, which includes 3 doses vaccine fee, administration and patient time cost. The HPV vaccine cost in the public and private sector were used to estimate the range of the HPV vaccination ($664 to $814). The annual probabilities of HPV vaccination coverage among 12 to 26-year-old females were derived from the CDC's Morbidity and Mortality Weekly Report and Chesson et al. (2019) study. In both studies, they used the National Immunization Survey-Teen (NIS-Teen) data to estimate vaccination coverage. NIS-Teen is a survey used to estimate the annual vaccination coverage among adolescents in the U.S.[3,13]

HPV 16/18 and other high-risk types infection

Data on the incidence of HPV 16/18 and other high-risk infections were derived from the literature. [14] That research followed a female cohort aged 15-85 years old (N=1,610) with negative HPV infections and normal cytological results at the baseline and every 6 months for an average of 4.1 years. Study found that the incidence of all HPV high-risk type infections was 5.0 cases/100 woman-years. The incidence of HPV 16 and 18 type infections were 1.0 and 0.7 cases/100 woman-years, respectively.

We derived the progression and regression of incident HPV infection from a study by Insinga et al. (2007). [15] A cohort of 16-23 years old females (N=2,391) was followed every 6 months for 4 years. Results for the 12-month HPV 16 type infection regressed to negative infection, progressed to CIN I, II, and III, were 0.354, 0.105, 0.045, and 0.024, respectively.

LSIL and HSIL

Data on the transition probabilities of SIL were derived through a meta-analysis of published studies. [16]. The conclusion was that the 6-month transition probability of HSIL to cancer was 0.0037. For the LSIL, the 6-month transition probabilities were 0.074 and 0.036 for the regression rate to normal and the progression rate to HSIL, respectively. We assumed no prevalent LSIL and HSIL existed in the initial cohort population.

Cervical cancer

Cervical cancer is classified by three stages: local cervical cancer, regional cervical cancer, and distant cervical cancer. Data on transition probabilities related to cervical cancer, including progression rate to a more severe stage, symptom detection, and stage-specific cancer mortalities, were derived from the literature. [17,18]. Patients underwent treatment after cancer detections and were defined as cancer survivors.

Utility

The utility weight of HPV infection is assumed to be 1, as it is asymptomatic. [4]. The quality of life weights for females diagnosed with LSIL, HSIL and local stage cancers were derived from the published literature.[19]. In that work, researchers interviewed 276 females to measure utility scores for HPV vaccination, CIN I-III, and early cancer stage using EQ5D. Females diagnosed at the regional stage were assumed to have a quality of life assessments of 0.67.[20]. Quality of life weight for the distant cancer stage was assumed to be 0.48, using 25th percentiles for quality of life scores among 27 females found having genital cancer [21].

Results

Base-case analysis results

We compared costs and effectiveness of interventions involving the patient reminder and recall system, patient education, provider reminder, school-based vaccine programs, reducing out-of-pocket costs, and intervention combinations versus current practice. The parameters of costs and effectiveness used in the base-case and sensitivity analysis are presented in Table 10. Interventions, except the current practice were ordered from lowest to highest costs. Under base-case conditions, we found that patient reminder and recall system was cost-saving, compared with current practice. The cost of implementing patient reminder and recall systems were lower than current practice and yielded better QALYs outcome (Table 11). Interventions of both provider reminder and patient education were dominated by patient reminder and recall system since it has higher costs but the lower effectiveness than patient reminder and recall system. The ICER of reducing out-of-pocket costs were $196,164. The school-based vaccine

programs were dominated since they have higher costs but lower QALYs than the intervention combination. The intervention combination was extended dominance since the ICER of it was greater than reducing out-of-pocket costs.

Sensitivity analysis

Sensitivity analysis was performed to address uncertainties for main input parameters, including intervention costs, the intervention effectiveness, the HPV vaccine cost, incidence rates of HPV infections, cervical cancer stage-specific treatment costs and utility weights. Tornado diagrams of multiple one-way sensitivity analyses were presented (Figure 9 to 14). We found that intervention effectiveness has a greater impact on the ICER than intervention costs. When we varied the costs for each HPV vaccine promotion intervention, patient reminder and recall system remained the most cost-effective in the majority analysis. When the effectiveness of patient reminder and recall system was lower than 6%, provider reminder is the most cost-effective intervention. If the effectiveness of patient education was higher than 19%, patient education is the most cost-effective intervention. School-based vaccine programs and intervention combinations are the most cost-effective intervention when its effectiveness is higher than 21% and 29%, respectively. When we varied the cost of the HPV vaccine varied in the range of $664 to $814, patient reminder and recall systems remained the most cost-effective intervention.

Two-way sensitivity analyses were performed which costs and effectiveness of each intervention were varied simultaneously. The patient reminder and recall system remained the most cost-effective intervention in the majority analysis. However, if the cost for the intervention designed to reduce out-of-pocket costs decreased to $211/ per participant and its effectiveness is higher than 36%, it is more cost-effective than patient

reminder and recall system. If the cost for the intervention combinations decreased to $250/ per participant and effectiveness is higher than 42%, it is more cost-effective than the patient reminder and recall system. We examined the "best-case (the lowest cost and the highest effectiveness)" and "worst-case (the highest cost and the lowest effectiveness)" scenarios in the multiple-way sensitivity analysis (Table 12). In the best-case scenario, the most cost-effective intervention was intervention combinations. In the worst-case scenario, the most cost-effective was provider reminder. PSA was performed on the main input parameters using 1000 Monte-Carlo simulations with samples from defined distribution. Figure 15 displays the cost-effectiveness acceptability curve (CEAC), which illustrates the probability that the reducing out-of-pocket costs intervention will be cost-effective versus the patient reminder and recall system for a hypothetical set of decision-maker willingness to pay values. Interventions which were dominated or extended dominance in the base-case analysis, including provider reminder, intervention combinations, patient education and school-based vaccine programs were excluded in the CEAC analysis. If the willingness to pay is $25,000 per QALY, the probability that reducing out-of-pocket costs will be cost-effective relative to the patient reminder and recall system is 0. If the willingness to pay is $200,000 per QALY, the probability that reducing out-of-pocket costs will be cost-effective relative to the patient reminder and recall system is 52.4%.

Discussion

As the HPV vaccine coverage is suboptimal in the U.S., we have put many efforts into developing interventions to increase vaccine coverage. Resource consequences of developing HPV vaccine promotion interventions should be included in the evaluation of HPV vaccination programs. It is also important to determine what types of HPV

vaccine promotion intervention are most cost-effective in improving health outcomes. We conducted a CUA to evaluate HPV vaccine promotion interventions of vaccination programs. To our knowledge, this is the first study that examined alternative HPV vaccine promotion interventions in the evaluation of HPV vaccination.. The audience of this study includes health promotion intervention planners and decision-makers who select the intervention within their resource and budgetary constraints.

We compared 6 HPV vaccine promotion interventions—the patient reminder and recall system, patient education, provider reminder, school-based vaccine programs, reducing out-of-pocket costs and intervention combination versus current practice. Study shows that implementing patient recall and reminder system is the most cost-effective intervention of the HPV vaccination programs. Implementing patient reminder and recall system is cost-saving to the HPV vaccination program, compared with current practice. The intervention designed to reduce patient out-of-pocket costs was more effective in improving health outcomes than the patient reminder and recall system but substantially increased the cost. Decision-makers need to consider the applicability of interventions (e.g. different population or settings) and budgets for implementing the interventions to determine which intervention would be justified and feasible. Social and political issues need to be discussed by stakeholder groups, including parents, adolescents, pediatricians, school administrators and community before HPV vaccine promotion interventions are successfully implemented.

To validate our model simulations, we compared our lifetime cost estimates and QALYs with published researches which also used the Markov model to evaluate the HPV vaccination program in the U.S. (Table 13). [4,22,23] Our study shows the lifetime cost estimate ranged from $7,450 to $7,900, depending on the intervention strategies.

Costs range widely from $600 to $39,000 in the literature and our estimates are within the range. QALYs estimates in our study ranged from 28.4868 years of current practice to 28.4959 years of reducing out-of-pocket costs. The result is similar across prior research that shows the QALYs estimate ranging from 26 to 29 years gained per woman [4,22,23].

The main limitation of the study is the lack of data sources for some parameters. The effectiveness of the HPV vaccine completion rate for the school-based vaccine programs was not available in the literature. We used an alternative outcome HPV vaccine initiation rate in the base-case analysis. The cost data on both provider reminders and intervention combinations were not available in the literature. We applied the cost of interventions intended to increase other immunizations (eg. influenza or pneumococcal) from the Community Guide reports. Therefore, our model should be updated when the cost data is available. Secondly, our Markov model does not take into account the impact of the vaccination on herd immunity, making our results conservative. Prior studies using the dynamic transmission model that accounted for herd immunity effects have shown that ICER for HPV vaccination program would be even lower. Thirdly, we did not include all of the HPV vaccine promotion interventions because of the lack of both cost and effectiveness data in the literature. Interventions include the provider assessment and feedback, vaccination requirements for school attendance, standing orders and immunization information systems were excluded from our analysis. Extending our analysis to include those interventions when data is available is needed.

Conclusions

A CUA was conducted to assess HPV vaccine promotion interventions of cervical cancer in the U.S. The study shows that implementing patient recall and reminder system is the most cost-effective intervention of the HPV vaccination programs. Compared with current practice, patient recall and reminder system is cost-saving since the cost is lower and yields a better health outcome. Decision-makers need to consider the applicability of interventions and budgets for implementing the interventions. Social and political issues need to be discussed by stakeholder groups before HPV vaccine promotion interventions are successfully implemented.

Figure 8. States and allowed transitions of natural history of cervical cancer

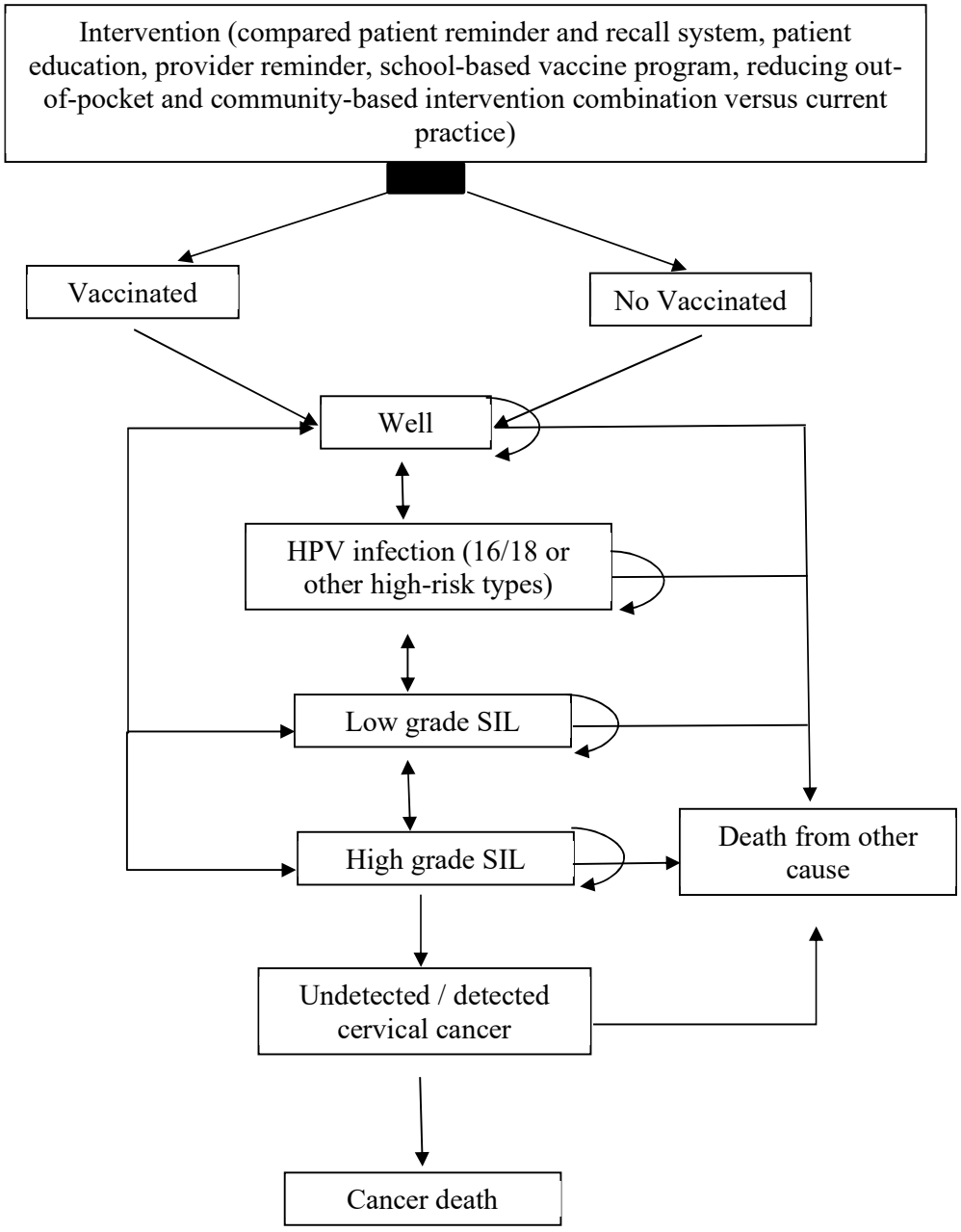


Table 9. The CHEERS checklist of the study

Section/item	Item No	Recommendation	Reported on page No
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	79
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Abstract page
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	79
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analyzed, including why they were chosen.	80
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	80
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	80
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	80
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	80
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	80
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	80
Measurement of effectiveness	11	Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	81
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	83
Estimating resources and costs	13	Single study-based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary	81

		research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	80
Choice of model	15	Describe and give reasons for the specific type of decision analytical model used. Providing a figure to show model structure is strongly recommended.	80
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	80
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	80
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	93
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	96
Characterizing uncertainty	20	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	84
Characterizing heterogeneity	21	If applicable, report differences in costs, outcomes, or cost- effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	NA

Study findings, limitations, generalizability, and current knowledge	22	Summarize key study findings and describe how they support the conclusions reached. Discuss limitations and the generalizability of the findings and how the findings fit with current knowledge.	87
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	NA
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	NA

Table 10. Input values and sources for transition probabilities in the model

Parameter	Base-case	Range	Source
HPV vaccine coverage increased by HPV promotion interventions			
current practice	+2%	NA	[24]
Patient reminder and recall system	+10%	0~25%	[25–27]
Patient education	+7%	0~25%	[28–32]
Provider reminder	+8%	+8%~+17%	[24,28,33]
Vaccination programs in school	+5%	+5%~+41%	[34–36]
Reducing out-of-pocket costs	+28%	+10%~+45%	[28,37,38]
Community-based intervention combination	+13%	+2%~+56%	
Intervention cost (2018 USD)			
Current practice	$3	0~$6	[39]
Patient reminder and recall system	$22	$2~$33	[40,41]
Patient education	$73	$37~$90	[39]
Provider reminder	$29	$8~$62	[33]
Vaccination programs in school	$85	$43~$128	[35]
Reducing out-of-pocket costs	$575	$40~$724	[39,42,43]
Intervention combination	$133	$63~$313	[44]
Cost			
HPV vaccine	$739	$664~$814	[12,45]
Treatment for LSIL	$2,331		[13,18]
Treatment for HSIL	$5,165		[13,18]
Treatment for cervical cancer local stage	$38,260		[46]
Treatment for cervical cancer reginal stage	$40,948		[46]
Treatment for cervical cancer distant stage	$65,585		[46]
HPV vaccine			
Baseline HPV vaccine coverage in 12 years old females [a]	38.9%		[3]

Annual probability on HPV vaccination in 13-18 years old females	0.129	[13]
19-26 years old females	0.026	[13]
Vaccine efficacy (%)	100.00%	Assumption
HPV types 16/18 infection		
Incidence of HPV 16 infection	0.010	[14]
Incidence of HPV 18 infection	0.007	[14]
Regression to negative HPV 16/18 infection	0.354	[15]
HPV 16/18 infection progressed to CIN I	0.105	[15]
HPV 16/18 infection progressed to CIN II	0.045	[15]
HPV 16/18 infection progressed to CIN III	0.024	[15]
Proportion of HPV 16/18 infection	0.135	[13]
HPV other high-risk infection		
Incidence of HPV other high-risk infection	0.050	[14]
Regression to negative HPV other high-risk infection	0.403	[47]
HPV other high-risk infection progressed to CIN I	0.063	[47]
HPV other high-risk infection progressed to CIN II	0.032	[47]
HPV other high-risk infection progressed to CIN III	0.004	[47]
LSIL		
Developing HSIL from LSIL	0.071	[16]
LSIL regressed to well	0.143	[16]
HSIL		
Prevalence of HSIL in the initial cohort	0	Assumption
Developing cervical cancer stage I from HSIL	0.007	[16,48]
HSIL regressed to well	0.296	[48]
HSIL regressed to LSIL	0.056	[16]
Cervical cancer		
Progression from local stage to reginal stage	0.215	[17]

Progression from reginal stage to distant stage	0.262	[17]
Mortality of local stage in year 1	0.019	[17]
year 2-3	0.017	[17]
year 4-20	0.011	[17]
Mortality of reginal stage in year 1	0.108	[17]
year 2-3	0.090	[17]
year 4-20	0.042	[17]
Mortality of distant stage in year 1	0.300	[17]
year 2-3	0.210	[17]
year 4-20	0.087	[17]
Probability of symptom detection for local stage	0.190	[17]
Probability of symptom detection for reginal stage	0.600	[17]
Probability of symptom detection for distant stage	0.900	[17]
Utility		
HPV infection	1.00	[4]
LSIL	0.972	[19]
HSIL	0.970	[19]
Cervical cancer local stage	0.818	[19]
Cervical cancer reginal stage	0.67	[18]
Cervical cancer distant stage	0.48	[18]
Cervical cancer survivor	0.76	[18]
Discount rate	0.03	Assumption
Markov model cycle length	1 year	Assumption

a: HPV up-to-date rate among 13 years females in 2018

Table 11. Cost-effectiveness of HPV vaccine promotion interventions

Strategy[a]	Cost	Incremental cost	QALY(yrs)	Incremental Effectiveness	ICER	C/E
Current practice	7861.14	-	28.4868	-	-	275.96
Patient reminder and recall system	7449.56	-411.58	28.4936	0.0068	Cost-saving	261.45
Provider reminder	7491.59	42.03	28.4931	-0.0005	Dominated	262.93
Intervention combinations	7615.80	166.24	28.4928	-0.0008	Dominated	267.29
Patient education	7616.16	166.60	28.4942	0.0006	Extended dominance	267.29
School-based vaccine programs	7702.22	86.06	28.4921	-0.0021	Dominated	270.33
Reducing out-of-pocket costs	7900.02	450.46	28.4959	0.0023	$196,164	277.23

a: Interventions were ordered from the lowest to the highest cost

Figure 9. Tornado diagram of ICER: patient reminder vs. current practice

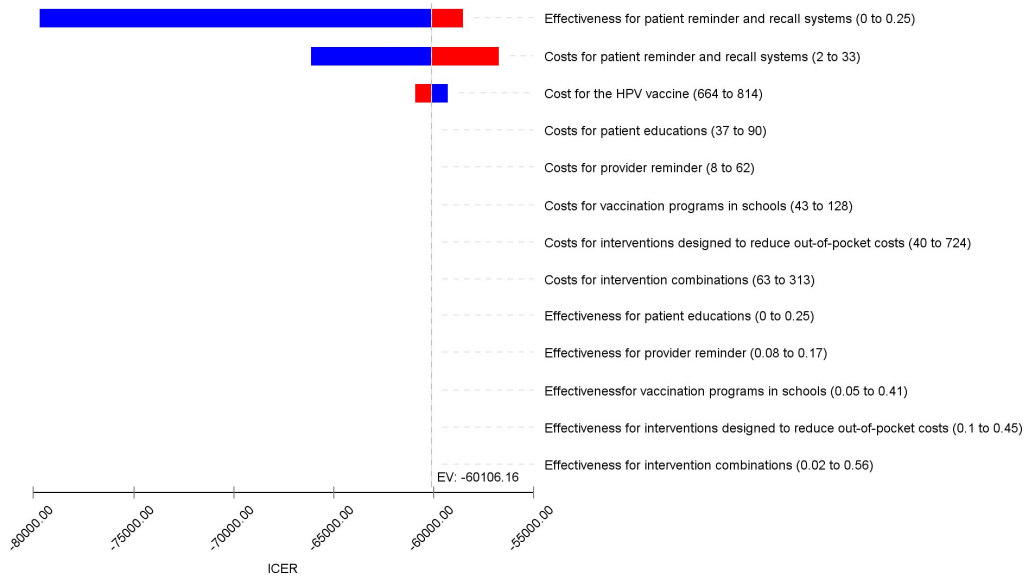


Figure 10. Tornado diagram of ICER: patient education vs. current practice

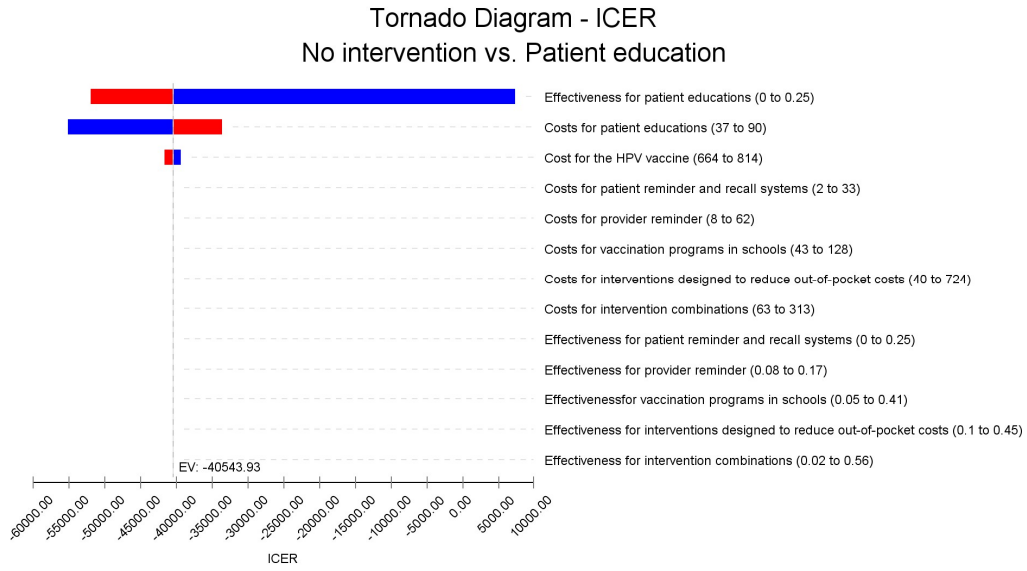


Figure 11. Tornado diagram of ICER: provider reminder vs. current practice

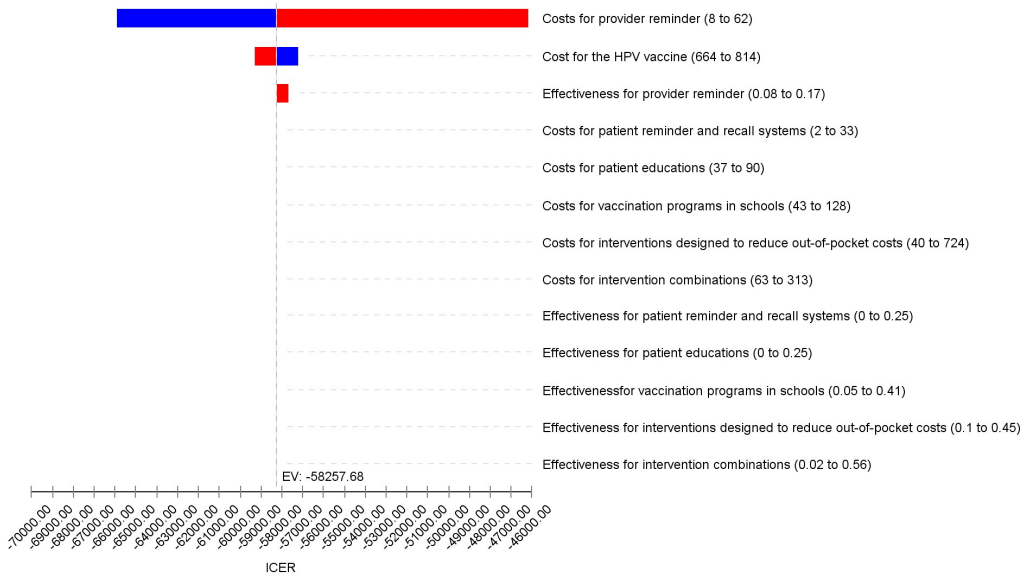


Figure 12. Tornado diagram of ICER: school-based vaccine programs vs. current practice

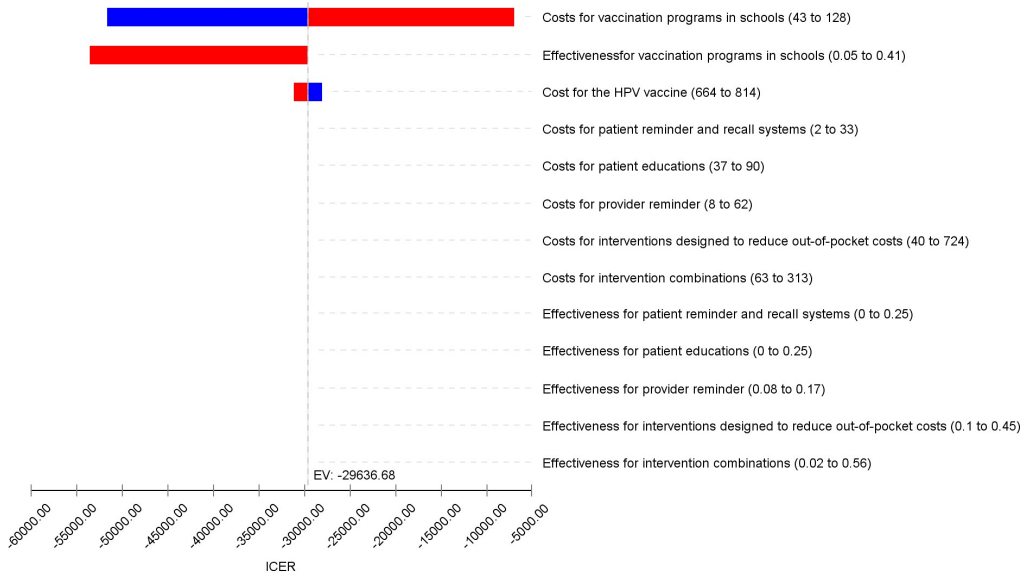


Figure 13. Tornado diagram of ICER: reducing out-of-pocket costs vs. current practice

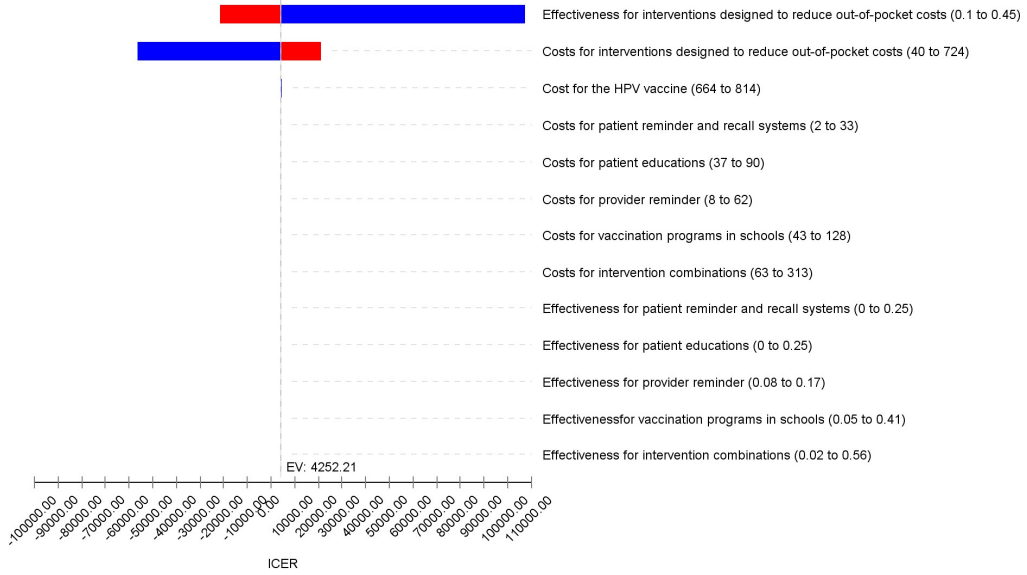


Figure 14. Tornado diagram of ICER: intervention combinations vs. current practice

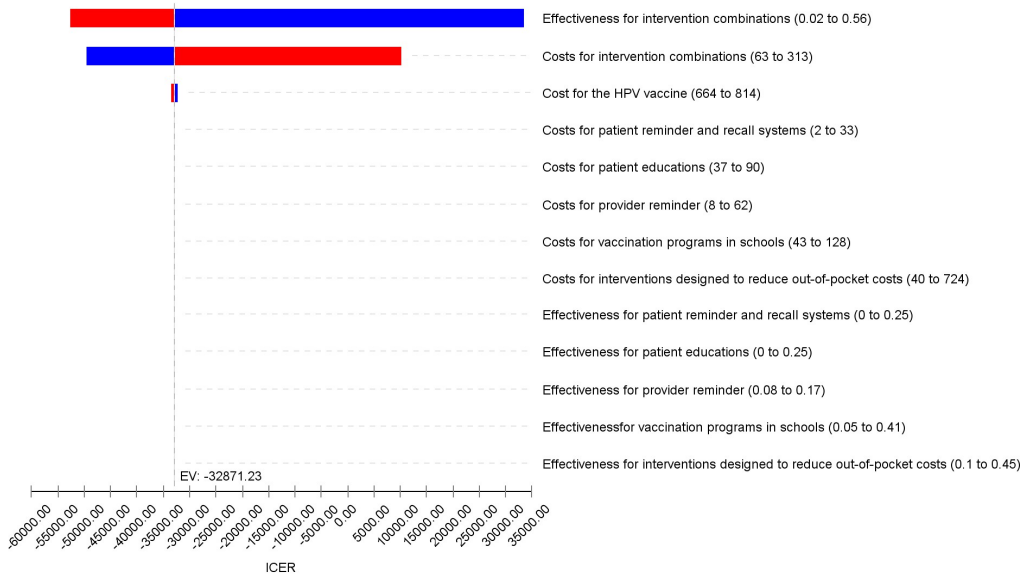


Table 12. Results of the multiple-way sensitivity analysis for HPV vaccine promotion interventions in the CUA

Strategy[a]	Cost	Incremental cost	QALY(yrs)	Incremental Effectiveness	ICER	C/E
The best-case scenario: the lowest costs and the highest effectiveness of HPV vaccine promotion interventions						
Current practice	7847.69	-	28.4868	-	-	275.49
Intervention combinations	7277.34	-570.34	28.4972	0.0104	Cost-saving	255.37
Reducing out-of-pocket costs	7288.41	11.07	28.4968	-0.0004	Dominated	255.76
School-based vaccine programs	7301.05	23.71	28.4966	-0.0005	Dominated	256.21
Patient reminder and recall system	7316.70	39.35	28.4957	-0.0015	Dominated	256.77
Patient education	7356.48	79.14	28.4957	-0.0015	Dominated	258.16
Provider reminder	7364.25	86.90	28.4948	-0.0023	Dominated	258.44
The worst-case scenario: the highest costs and the lowest effectiveness of HPV vaccine promotion interventions						
Current practice	7888.04	-	28.4868	-	-	276.90
Provider reminder	7568.06	-319.98	28.4931	0.0063	Cost-saving	265.61
Patient reminder and recall system	7702.05	133.99	28.4894	-0.0037	Dominated	270.35
School-based vaccine programs	7823.60	255.54	28.4921	-0.0010	Dominated	274.59
Patient education	7956.23	388.18	28.4894	-0.0037	Dominated	279.27
Intervention combinations	8644.80	1076.74	28.4907	-0.0024	Dominated	303.43
Reducing out-of-pocket costs	8903.14	1335.08	28.4936	0.0005	Dominated	312.46

Table 13. Comparisons with the CEA results between literature using Markov model in evaluating HPV vaccine in the US.

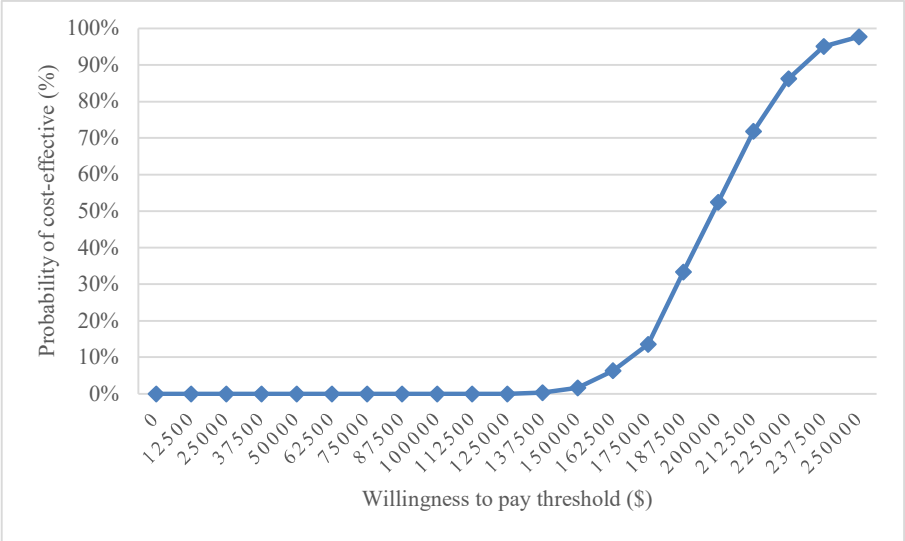
Author (year)	Target population	HPV vaccine coverage assumption	Results for the economic evaluation on HPV vaccination	Epidemiology outcomes for HPV vaccination
Sanders and Taira (2003) [4]	12 years old girls through lifetime	70% of vaccine coverage	Cost for the standard of care without vaccination: $39,682 Cost for the standard of care with vaccination: $39,928 QALYs for the standard of care without vaccination: 27.720 (yrs) QALYs for the standard of care with vaccination: 27.731 (yrs) ICER between two above strategies =$22,755/QALY gained	Averts more than 224,255 cases of HPV, 112,710 cases of SIL, 3,317 cases of cervical cancer when vaccinating the population of approximately 1,988,600 girls
Kulasingam and Myers (2003) [22]	12 years old girls through 85 years old	100% of vaccine coverage	Cost of screening every 3 years for 18 years old females without vaccination: $632 Cost of screening every 2 years for 24 years old females with vaccination: $834 LYs of screening every 3 years for 18 years old females without vaccination: 28.7518 (yrs) LYs of screening every 2 years for 24 years old females with vaccination: 28.7563 (yrs) ICER between two above strategies=$44,889/LY gained	Reduced cervical cancer incidence by 82.6% when vaccinating the target population
Goldie et al. (2004) [23]	13 years old girls through lifetime	100% of adolescent cohort is	Cost of standard of care without vaccination: $1,111	Reduced the lifetime risk of cervical cancer by 66%

successfully vaccinated	Cost of standard of care with vaccination: $1,384 QALYs for the standard of care without vaccination: 25.9815 (yrs) QALYs for the standard of care with vaccination: 25.9948 (yrs) ICER between two above strategies =$20,600/QALY gained	when efficacy of HPV vaccine is 100%

Abbreviation: ICER, Incremental cost-effectiveness ratio; SIL, Squamous intraepithelial lesions; QALYs, Quality-adjusted-life-years; LYs, Life-years

A: Standard of care included routine Pap tests for every 2 years starting at age

Figure 15. Cost-effectiveness acceptability curve compare reducing out-of-pocket costs versus patient reminder and recall system



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CONCLUSION

A total of 56 studies for the HPV vaccine promotion intervention were included in the study. Intervention approaches used to improve HPV vaccine coverage included patient reminder and recall systems, patient education, provider assessment and feedback, provider reminders, reducing out-of-pocket costs, school-based vaccine programs, vaccination requirements for school attendance, standing orders, immunization information systems and multiple component interventions (interventions implemented in combination involved more than two interventions). Most interventions significantly increased HPV vaccine rates using varied approaches across populations and settings, and with modest cost. A cost-effectiveness analysis was conducted to assess those HPV vaccine promotion interventions. We assessed interventions which their cost and effectiveness are available across literature. We included patient reminder and recall system, patient education, provider reminders, reducing patient out-of-pocket costs, school-based vaccine programs, and community-based intervention combinations in the economic evaluation. We found that patient reminder and recall system is the most cost-effective HPV vaccine promotion interventions. The cost per additional individual completed HPV vaccine series (ICER) was $238. When the intervention effectiveness was measured as the percentage change of receiving at least one dose HPV vaccine, the ICER for the patient reminder and recall system was $107. When we incorporated cervical cancer natural history, cost and quality of life for cervical cancer, patient recall can reminder system is cost-saving since the cost is lower and yields a better health outcome, compared with current practice. The study provides evidence-based information to decision-makers about interventions aimed to improve HPV vaccine coverage.

APPENDICES

Table 1. Searching keywords

Concepts	Key words used fir searching
human papillomavirus	papillomaviridae/ or alphapapillomavirus/ or human papillomavirus 6/ or human papillomavirus 11/ or human papillomavirus 16/ or human papillomavirus 18/ or human papillomavirus 31/ or betapapillomavirus/ or gammapapillomavirus/ or mupapillomavirus/ (hpv or papillomavirus or papillomaviridae or alphapapillomavirus or betapapillomavirus or mupapillomavirus or genital warts or epidermodysplasia verruciformis or condyloma*).ti,ab,kw. papillomavirus infections/ or warts/ or condylomata acuminata/ or buschke-lowenstein tumor/ or epidermodysplasia verruciformis/
vaccine	vaccines/ or viral vaccines/ or immunization/ or immunization schedule/ or immunization, secondary/ or immunotherapy/ or immunotherapy, active/ or vaccination/ or mass vaccination/ or immunization programs/ or (vaccin* or immuniz* or immunis*).ti,ab,kw.
intervention	public health/ or school education/ or Epidemiology/ or prevent/ or preventing/ or prevention/ or protect/ or protects/ or protecting/ or protection/ or public health/ or education/ or program/ or train/ or training/ or support/ or project/ or (educat* or program* or intervent*).ti,ab,kw.

Table 2:Ovid Medline® search strategy

Provider/Interface	Ovid
Database	Medline®
Date searched	2017/7/28
Database update	
Search developer(s)	Chi-Fang Wu and Helena M. VonVille
Limit to English	Yes
Date Range	2006-2017
Search filter source	http://libguides.sph.uth.tmc.edu/search_filters/topics-filters

#	Searching key words	Item found
1.	vaccines/ or viral vaccines/ or immunization/ or immunization schedule/ or immunization, secondary/ or immunotherapy/ or immunotherapy, active/ or vaccination/ or mass vaccination/ or immunization programs/ or (vaccin* or immuniz* or immunis*).ti,ab,kw.	275136
2.	papillomaviridae/ or alphapapillomavirus/ or human papillomavirus 6/ or human papillomavirus 11/ or human papillomavirus 16/ or human papillomavirus 18/ or human papillomavirus 31/ or betapapillomavirus/ or gammapapillomavirus/ or mupapillomavirus/	21893
3.	(hpv or papillomavirus or papillomaviridae or alphapapillomavirus or betapapillomavirus or mupapillomavirus or genital warts or epidermodysplasia verruciformis or condyloma*).ti,ab,kw.	38627
4.	papillomavirus infections/ or warts/ or condylomata acuminata/ or buschke-lowenstein tumor/ or epidermodysplasia verruciformis/	24206
5.	2 or 3 or 4	43340
6.	1 and 5	10673
7.	papillomavirus vaccines/ or human papillomavirus recombinant vaccine quadrivalent, types 6, 11, 16, 18/	6240
8.	6 or 7	11300
9.	public health/ or school education/ or Epidemiology/ or prevent/ or preventing/ or prevention/ or protect/ or protects/ or protecting/ or protection/ or public health/ or education/ or program/ or train/ or training/ or support/ or project/ or (educat* or program* or intervent*).ti,ab,kw.	1474261

10	8 and 9	3414
11.	limit 10 to (english language and yr="2006 - 2017")	3088
12.	(11 and exp united states/) or (11 not (exp africa/ or exp asia/ or exp australia/ or exp canada/ or exp europe/ or exp south america/))	1892

Table 3: PubMed search strategy

Provider/Interface	National Library of Medicine
Database	PubMed
Date searched	2017/07/31
Database update	
Search developer(s)	Chi-Fang Wu and Helena M. VonVille
Limit to English	Yes
Date Range	2006-2017
Search filter source	http://libguides.sph.uth.tmc.edu/search_filters/topics-filters

#	Searching key words	Item found
1	vaccines[mesh:noexp] OR viral vaccines[mesh:noexp] OR immunization[mesh:noexp] OR immunization schedule[mesh:noexp] OR immunization, secondary[mesh:noexp] OR immunotherapy[mesh:noexp] OR immunotherapy, active[mesh:noexp] OR vaccination[mesh:noexp] OR mass vaccination[mesh:noexp] OR immunization programs[mesh:noexp] OR (vaccin*[tiab] OR immuniz*[tiab] OR immunis*[tiab])	405181
2	papillomaviridae[mesh:noexp] OR alphapapillomavirus[mesh:noexp] OR human papillomavirus 6[mesh:noexp] OR human papillomavirus 11[mesh:noexp] OR human papillomavirus 16[mesh:noexp] OR human papillomavirus 18[mesh:noexp] OR human papillomavirus 31[mesh:noexp] OR betapapillomavirus[mesh:noexp] OR gammapapillomavirus[mesh:noexp] OR mupapillomavirus[mesh:noexp]	27400
3	(hpv[tiab] OR papillomavirus[tiab] OR papillomaviridae[tiab] OR alphapapillomavirus[tiab] OR betapapillomavirus[tiab] OR mupapillomavirus[tiab] OR genital warts[tiab] OR epidermodysplasia verruciformis[tiab] OR condyloma*[tiab])	45495
4	papillomavirus infections[mesh:noexp] OR warts[mesh:noexp] OR condylomata acuminata[mesh:noexp] OR buschke-lowenstein tumor[mesh:noexp] OR epidermodysplasia verruciformis[mesh:noexp]	28500
5	#2 OR #3 OR #4	54252
6	#1 AND #5	10713
7	papillomavirus vaccines[mesh:noexp] OR human papillomavirus recombinant vaccine quadrivalent, types 6, 11, 16, 18[mesh:noexp]	5765
8	#6 OR #7	11291
9	public health[mesh:noexp] OR school education[mesh:noexp] OR Epidemiology[mesh:noexp] OR prevent[mesh:noexp] OR preventing[mesh:noexp] OR prevention[mesh:noexp] OR protect[mesh:noexp] OR protects[mesh:noexp] OR	658273

	protecting[mesh:noexp] OR protection[mesh:noexp] OR public health[mesh:noexp] OR education[mesh:noexp] OR program[mesh:noexp] OR train[mesh:noexp] OR training[mesh:noexp] OR support[mesh:noexp] OR project[mesh:noexp] OR intervention OR (educat *[tiab] OR program *[tiab] OR intervent *[tiab])	
10	#8 AND #9	697
11	#10 AND (english[la] AND 2006:2017[dp])	617
12	(#11 AND (north america[mesh:noexp] OR united states[mesh])) OR (#11 NOT (africa[mesh] OR asia[mesh] OR australia[mesh] OR canada[mesh] OR europe[mesh] OR south america[mesh]))	422

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