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Effective HPV Vaccination Strategies: What Does the Evidence Say? An Integrated Literature Review

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ABSTRACT

Problem: The updated Advisory Committee on Immunization Practices (ACIP) 2016 guidelines recommends vaccination for the human papillomavirus (HPV) for all adolescents starting at ages 11–12 years. The United States continues to fall short of the benchmarks set by Healthy People 2020. The national vaccination rates hover at 49.5%, creating much room for improvement in health care systems. The purpose of this literature review was to identify evidence-based interventions to implement for improved outcomes.
Eligibility Criteria: An integrative literature review was conducted using the CINAHL, EBSCO, Academic Search Complete, ProQuest and Medline databases. The search was limited to studies published in peer reviewed journals in the last 10 years.
Sample: Of the available studies, 201 met inclusion criteria with 46 studies meriting further review.
Results: Barriers to vaccination included missed opportunities due to lack of provider recommendation and awareness of current guidelines, and parental vaccination hesitancy. Effective strategies included reminder systems and strong provider recommendations.
Conclusions: No one method has been effective in maintaining increases in vaccination rates. Multi-method strategies demonstrate the highest rates of maintaining increases in HPV vaccination. Strong provider recommendations are a cornerstone to any multi-method intervention.
Implications: Providers and nurses need to shift conversations to strong recommendations for the HPV vaccination and include additional reminder systems, including protocols to meet Healthy People 2020 goals for HPV vaccination.

Introduction

As the most common sexually transmitted infection in the United States, the human papillomavirus (HPV) poses major health risks for adolescents (Kasting et al., 2016). The impact of this infectious disease is not realized until years after the infection. Human papillomavirus has been associated with approximately 33,000 cancers each year (Perkins et al., 2015). Although the majority of HPV related cancers account for 96 to 98% of cervical cancers, HPV also is associated with up to 93% of anal cancers, 63% of oropharyngeal cancers, 40% of penile cancers, and 51% of vaginal cancers (Thomas, 2016). There has been a notable increase in oropharyngeal cancer rates in young adults caused by HPV types 16 and 18 (Chaturvedi et al., 2011).

The annual financial costs associated with HPV cancers are estimated at 7 billion dollars (Perkins et al., 2015). The HPV infection rate in 2015 has been estimated at up to 93% in males over age 19, and at 45% for females between the ages of 14 to 59 years (Thomas, 2016). Initial HPV vaccination was approved for females in 2006, with marketing focused on prevention of cervical cancers. This approach has left the male adolescent population unprotected and has allowed further spread of HPV in both male and female populations.

The 9-valent HPV vaccine, which protects against nine of the most common cancer strains (HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58), was approved by the Food and Drug Administration (FDA) in 2014 for use in all adolescents starting as early as age nine (Kasting et al., 2016). Extensive testing has demonstrated efficacy with two doses, if given before age 15 years. After age 15, immunocompetence requires three doses to be administered. In 2016, the Advisory Committee on Immunization Practices (ACIP) updated the HPV vaccine recommendations to include males, starting at ages 11 to 12 years, using the two-dose schedule with the 9-valent vaccine (Meites, Kempe, & Markowitz, 2016). Despite the recent guideline changes, many providers delay or do not recommend HPV vaccination in adolescents ages 11 to 12 years, resulting in current U.S. HPV vaccination rates of 49.5% for

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females and 37.5% for males between the ages of 13 and 17 years (Centers for Disease Control and Prevention, 2017). These vaccination rates are much lower than other countries such as Australia (71.2%) and the United Kingdom (60.4%) (National Cancer Institute, 2014).

Delaying or missing opportunities to vaccinate adolescents is concerning when considering the high-risk sexual behaviors occurring throughout the nation in this population group. The annual Centers for Disease Control (CDC) Youth Risk Behavior Survey (YRBS) data from 2015 provides valuable data about sexual practices in adolescents. The 2015 survey results, from grades 9 through 12, found that 4% had sexual intercourse for the first time before age 13 years, 12% had sexual intercourse with four or more persons during their life, and 43% did not use a condom during last sexual intercourse (Center for Disease Control and Prevention, 2016). Further evidence demonstrates that males have a higher oral HPV type 16 prevalence and are more likely to have multiple sexual partners (D'Souza, Cullen, Bowie, Thorpe, & Fakhry, 2014). With these high-risk behaviors, and HPV the most common sexually transmitted infection, vaccination should be a priority for health promotion interventions in the adolescent population.

Purpose

Due to the low rates of HPV vaccination nationwide, there is a need to identify effective strategies that increase vaccination uptake and completion rates. As HPV infection presents long-term health risks, it is critical to improve approaches for this cancer prevention intervention in practices serving the adolescent population. This literature review explores the current state of available evidence to identify effective strategies for improving outcomes of HPV vaccination completion.

Methods

An integrative literature review was conducted through the CINAHL, EBSCO, Academic Search Complete, ProQuest and Medline databases using the keywords human papillomavirus, HPV, HPV and cancer, HPV and oropharyngeal cancer, HPV vaccine, HPV immunization, vaccine hesitancy, barriers to immunization, motivational interviewing, announcement technique, health belief model and vaccination, vaccination compliance and vaccination uptake interventions. Reference lists from applicable studies were reviewed for additional studies not identified in the search results. The search was limited to studies published in peer-reviewed journals in the last 10 years. This search strategy identified 201 studies that met inclusion criteria, with 46 studies meriting further review. The review focused on U.S. population groups, although two international studies (Sweden and Canada) were included under provider recommendation interventions. Studies were evaluated using the Melnyk levels of evidence and John Hopkins evidence appraisal tool (John Hopkins Medicine, 2017; Melnyk & Fineout-Overholt, 2015). This integrative review included evidence levels I through VI following Melnyk and Fineout level of evidence table, with expert opinion articles excluded from the review (Fig. 1). Studies were then assessed for quality and level of evidence using John Hopkins evidence appraisal tool (Tables 1–3).

Results

The integrative review focused on interventions implemented to increase vaccination uptake. Barriers to vaccination and risk factors for HPV infection are also discussed, which adds to the understanding of the complex issues involved in HPV cancer prevention strategies. The study interventions reviewed include provider recommendation, text message reminders, and multi-method intervention strategies (Tables 1–3).

Risk Factors Associated With HPV

Human papillomavirus is transmitted through skin-to-skin contact with infected individuals. This includes vaginal, anal, and oral sexual contact (American Cancer Society, 2017). Individuals that practice high risk sexual behaviors increase their exposure exponentially. Data from the annual YRBSS identifies that adolescents are consistently practicing high risk sexual behaviors. Early sexual debut also places adolescents at higher risk for exposure to HPV infections (American Cancer Society, 2017; Center for Disease Control and Prevention, 2016). Multiple sexual partners, lack of barrier protection with sexual activity, and sexual identity exploration are specific risk factors in the adolescent populations (American Cancer Society, 2017; D'Souza et al., 2014; Fisher, Cahill, Tseng, & Robinson, 2016). Gender, age, and ethnicity have been found to be significant predictors of oral sexual behaviors, which is associated with higher prevalence of HPV infections. Once oral risk behavior is adjusted for, age and ethnicity are not predictors of oral HPV infection (D'Souza et al., 2014). Men are also 7 times more likely to have oral HPV type 16 infection, and 5 times more likely to develop HPV associated oral squamous cell carcinoma than women (D'Souza et al., 2014).

Barriers to Vaccination

There have been numerous barriers to vaccination identified in the literature. One commonly cited barrier is parental safety concerns, with 8% identified as lack of knowledge about the vaccine and 20% of parents reporting that the vaccine is unnecessary for their adolescent (Dorrell et al., 2014; Krakow et al., 2017). A multivariable logistic regression analysis found the most common reasons for not obtaining the HPV vaccination, in males between ages 13 and 17 years, included lack of provider recommendation (24.0%), vaccine was viewed as unnecessary (18.9%), lack of knowledge about HPV and the vaccine (16.4%), parental belief that the adolescent was not sexually active (8.1%), and safety concerns (7.3%) about the vaccine (Holman et al., 2014; Lu et al., 2015).

Safety concerns with HPV vaccine have been noted to be a cause for vaccine hesitancy. Misinformation about side effects and adverse reactions has added to the anti-vaccine movement. Vaccine side effects with HPV include similar profiles with other vaccines; mild pain at injection site, bruising, faintness and syncope from a vasovagal response causing sudden onset of hypotension (Zimet, Rosberger, Fisher, Perez, & Stupiansky, 2013). Despite these minimal side effects there is a plethora of misinformation that parents are exposed to, through unreliable internet sources (Tan, Lee, & Chae, 2015).

Additional parental concerns associated with vaccine hesitancy or refusal, is a fear that the adolescent would become sexually active once the HPV vaccination was completed. There have been numerous studies conducted that refute that concern. There is no evidence that demonstrates increased sexual risk behaviors in vaccinated adolescents (Madhivanan et al., 2016; Zimet et al., 2013).

Costs associated with the vaccination can also be a barrier to those who are uninsured or underinsured (Holman et al., 2014). The cost of the 9-valent HPV vaccine is $204.87 per dose in the private sector (Centers for Disease Control and Prevention, 2017). Many providers do not routinely store the vaccine in their offices due to this higher cost. Additionally the variability in insurance coverage for the vaccine has created hesitancy for the providers to recommend the vaccine before authorizing coverage from the insurance company (Bruno et al., 2014). There are inconsistent findings with school-based clinics administering the HPV vaccine. This strategy can address both cost reduction, through the VFC program, and access to the vaccine (Smulian, Mitchell, & Stokley, 2016). Further study is needed to evaluate if this would be an effective strategy to sustain a change in HPV vaccination uptake.

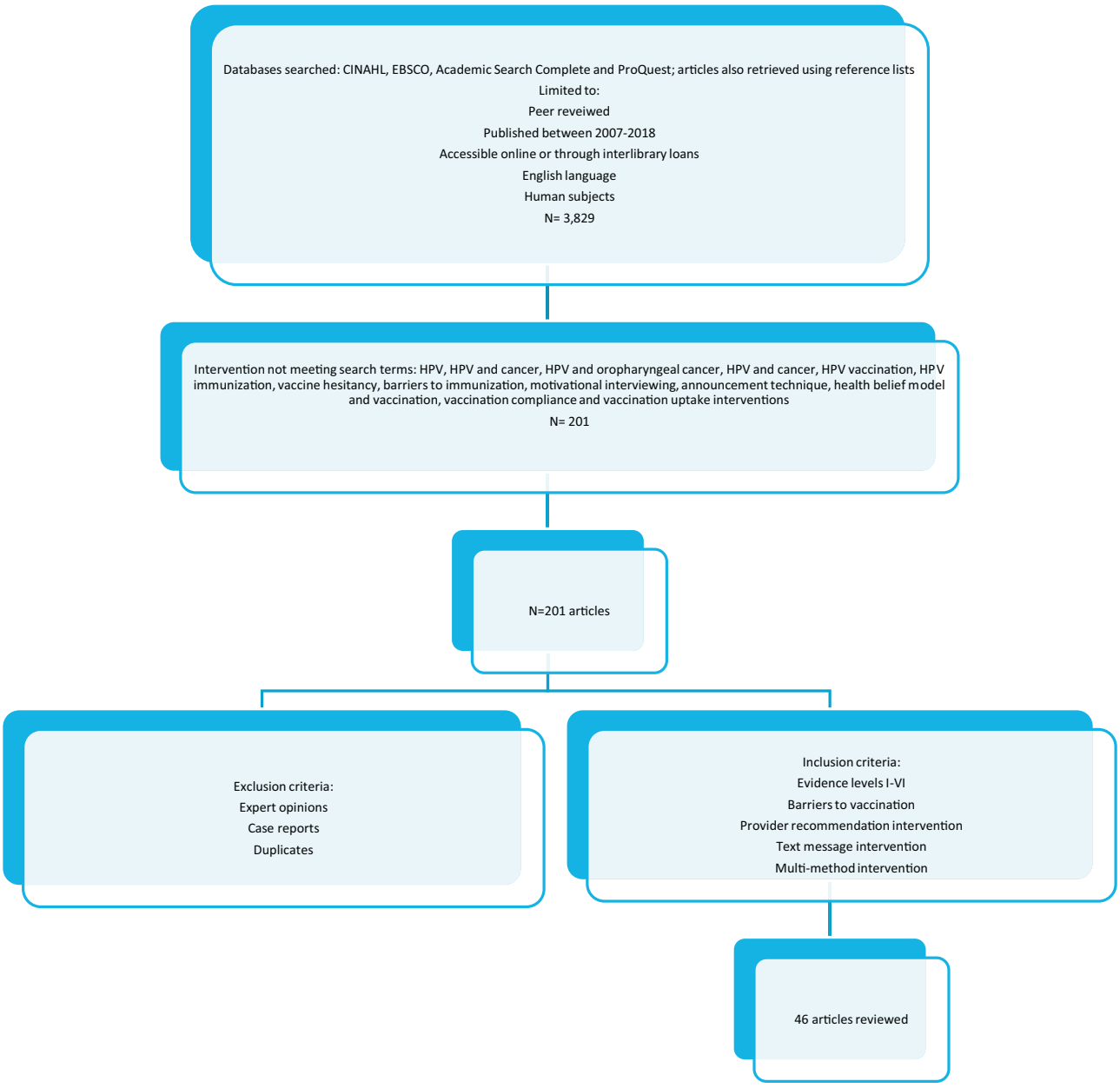

Fig. 1. Search strategies and review process.

Provider Recommendations

Awareness of HPV and the available vaccination was not found to correlate with vaccine uptake in low income populations (Fishman et al., 2016). Missed opportunities for vaccination are a significant barrier to reaching Healthy People 2020 vaccination goals (Office of Disease Prevention and Health Promotion, 2017). Provider recommendation for the HPV vaccination has been identified as a major component in vaccination uptake outcomes (American Cancer Society, 2017; Gilkey & McRee, 2016). Provider communication to the parents presented as a statement, assuming the parent will accept the recommendation to vaccinate, is categorized as announcement technique communication method. Announcement technique involves making statements with confidence, which often is perceived by the parent as more trustworthy. The conversational or informational communication technique, by the provider, is open-ended allowing invitation to the parent for discussion on the topic. Use of conversational communication technique can be effective in building rapport with the patient or family; however, it has not been found as effective in increasing vaccination uptake (Brewer et al., 2017; Moss et al., 2016). Announcement technique has been found to be the most effective, and a higher quality recommendation method to increase vaccination rates (Brewer et al., 2017; Gilkey & McRee, 2016).

A study conducted by Gilkey et al. (2016) explored provider recommendations for the HPV vaccine. They found that 48% received no recommendation for HPV vaccination. The study measured quality of provider recommendation through three quality indicators. The first measure was the strength of the recommendation, stating it was important to receive. The second indicator was educating that the vaccine prevents cancer. The third component was expressing the urgency for the vaccine, recommending same day vaccination. Each quality indicator received one point. Recommendations scoring 2–3 points were considered high quality, with low quality messages scoring 0–1 points. Of those that received recommendation, 16% were of low quality and

Table 1
Provider recommendations.

Author (s)	Purpose	Design/method	Sample description	Variables being studied	Results/findings	Level of evidence quality rating
Alexander, Best, Stupiansky, & Zimet, 2015	Identified provider recommendations practices post-ACIP change to recommend males receive HPV	Qualitative semi-structured interviews Grounded theory	20 pediatricians Convenience sample	(1) Knowledge (2) Skills and (3) Attitudes about HPV vaccination ACIP recommendation	Providers did not routinely recommend due to (1) Lack of knowledge (2) Lack of trust in vaccine effectiveness (3) Discomfort talking about STD's with younger population (4) Discomfort discussing sexual orientation with 11–16 year olds	Level 3 B
Bhatta & Phillips, 2015	Examined human papillomavirus (HPV) vaccine awareness and uptake, and communication with a parent and/or a health care provider	Cross sectional survey through 2012 Youth Risk Behavior Surveillance System (YRBSS). secondary data analysis of the modified 2012 Middle and High School Youth Risk Behavior Surveillance System (YRBSS) surveys	1299 participants, grades 6–12, 51.9% were male and 90.3% were white in rural Appalachian Ohio county	5 HPV-related questions included in the modified YRBS survey measuring (1) Provider recommendation for HPV vaccine, (2) HPV vaccine knowledge, and (3) Communication with parent related to HPV vaccine	(1) Despite the strong link between parental and health care provider communication and HPV vaccine uptake, the levels of communication remain low in this Appalachian population. (2) These findings suggest the need for public health education programs targeting the health care providers, the parents, and the adolescents to improve awareness, knowledge, and HPV vaccine uptake.	Level 3 B
Brewer et al., 2017	Evaluated for differences in method for introducing HPV vaccine and vaccine uptake	Parallel-group randomized clinical trial	30 pediatric and family medicine clinics in central North Carolina	(1) No training, (2) announcement technique training, and (3) conversation training impact on HPV vaccination uptake	(1) Six-month increases in HPV vaccination coverage were larger for patients in clinics that received announcement training versus those in control clinics (5.4% difference, 95% confidence interval: 1.1%–9.7%). (2) Stratified analyses showed increases for both girls (4.6% difference) and boys (6.2% difference). (3) Patients in clinics receiving conversation training did not differ from those in control clinics with respect to changes in HPV vaccination coverage.	Level 1 B
Bruno, Wilson, Gany, & Aragones, 2014	Explored provider practice, knowledge, and beliefs affecting HPV vaccination uptake	Cross-sectional survey	121 providers, 64% pediatricians, 19% internists, and 17% family practice specialists serving large minority populations	(1) Knowledge about HPV, HPV vaccine and cervical cancer, (2) Attitudes and beliefs toward the HPV vaccine, (3) Physician barriers to recommending HPV vaccines, (4) Perceived patient barriers for the HPV vaccine and (5) Systems that could improve current HPV vaccination rates	(1) 70% of providers cite lack of preventative care visits as barrier to recommendation for HPV vaccine. (2) Only 34% recommended HPV vaccine to eligible patients. (3) Pediatric providers (66%) were more likely to recommend HPV vaccine than family practice (27%) or internist providers (7%).	Level 3 B
Farmar et al., 2016	Evaluated effectiveness of HPV vaccination policy and procedure change on vaccine uptake	Regression analysis	11,463 subjects, between 13 and 17 years, average age was 14.77 years. Higher levels of Hispanic, English speaking, and <200% of the FPL	(1) Avoiding missed opportunities for vaccination and normalizing the HPV vaccine, (2) Bundling vaccinations for adolescents, and (3) Provider-level "report cards" with adolescent vaccination coverage rates	(1) HPV vaccination rates well above national uptake rates. (2) HPV coverage of ≥3 doses in 2014 was 66.8% for girls and 59.9% for boys.	Level 3 A
Fishman, Taylor, & Frank, 2016	Measured level of awareness among parents and adolescents about HPV and HPV	Longitudinal cohort study, using logistic regression methods	First cohort included low-income parents of females between ages of 9–18 years not vaccinated for HPV.	HPV vaccination status at 12 months compared to awareness levels of HPV and HPV vaccine	(1) <16% adolescents received the HPV vaccination during 12 month study. (2) The relationship between	Level 3 B

Table 1 (*continued*)

Author (s)	Purpose	Design/method	Sample description	Variables being studied	Results/findings	Level of evidence quality rating
	vaccine and impact of awareness on HPV vaccine uptake		Second cohort included females ages 13–18 years who had not been vaccinated for HPV.		awareness and subsequent vaccination was either not statistically significant or not meaningful in magnitude, with $R^2 = 0.004$ to 0.02. (3) The predicted probability of vaccine uptake was <0.50 for all awareness levels and prediction accuracy was poor (area under the curve = 0.56–0.64).	
Gilkey et al., 2016	Examined provider recommendations	Cross sectional survey, multivariable logistic regression models	1495 parents of 11 to 17 year old adolescents randomly selected using probability-based sampling approach.	(1) Provider recommendation for HPV vaccination (2) Quality of provider recommendation, and (3) HPV vaccination status	(1) 23% uptake when no provider recommendation compared to 74% uptake with high quality recommendation. (2) 48% received no recommendation. (3) Of those who received recommendation, 16% were low quality, and only 36% were high quality.	Level 3 A
Grandahl et al., 2017	Studied HBM and relationship for vaccine consent or not consent	Self-reported questionnaire	366 Swedish parents of children ages 11–12 years invited to complete survey with 200surveys completed	(1) Education, (2) Health beliefs (3) Education on vaccinations (4) sexual beliefs related to HPV vaccine	(1) 186 parents chose to vaccinate, with 14 choosing not to. No difference in characteristics between the two groups. (2) Education level of parent did not impact uptake (3) Refusals used internet as main source of information (4) Declining parents thought vaccine would increase sexual behavior/risk	Level 3 B
Kasting et al., 2016	Measured provider knowledge of new ACIP guidelines	Qualitative semi-structured interviews	22 health care providers, serving predominantly Medicaid population	(1) Knowledge about HPV vaccine and (2) Knowledge about the new ACIP guidelines	(1) Only 50% aware of the new HPV vaccine and recommendations. (2) Most did not think parents would have any additional questions about the vaccine (4-valent to 9-valent)	Level 3 B
Krakow, Beavis, Cosides, & Rositch, 2017	Identified characteristics of those not initiating HPV vaccination after provider recommendation	Secondary analysis, using Poisson regression, with the cross sectional 2014 National Immunization Survey-Teen. Survey (NIS-T)is conducted by CDC annually	12,742 surveys submitted by participants in the NIS-T annual survey in 2014	Provider recommendation for HPV vaccination and characteristics of population group not receiving HPV vaccination post-recommendation	(1) 2/3 of sample received provider recommendation ($n = 12,742$) (2) Large discrepancy in recommendations between genders, 74.3% females compared to 53.7% males (3) Of those receiving a recommendation, vaccination initiation rates higher in Hispanic males than in White males. No difference in uptake between African-American and White males. (4) Teens with no health visits in past year, and those who had not received no received Tdap booster were less likely (55%) to initiate HPV vaccination	Level 3 A
Krawczyk et al., 2015	Identified key differences between parents who obtain (acceptors) and parents who refuse (non-acceptors) the HPV vaccine for their daughters	Cross sectional survey	Convenience sample of parents in Quebec, Canada. 774 (92.8%) were included in the quantitative analyses. 95.7% parents of female adolescents, parents were 88.5% white. Parents' ages ranged from 26 to 58 (M D 40.2, SD D 5.97).	(1) Health Belief Model (HBM) association with HPV vaccination uptake. (2) Perception of risk, safety, and need for action. (3) Relationship between individual cognitive variables proposed by the HBM and uptake of the HPV vaccine.	Factors significantly related to HPV vaccine uptake included (1) Perceived barriers ($p < .01$) (2) Perceived safety ($p < .001$) (3) cues to action ($p < .001$), and (4) knowledge ($p < .01$). (5) White/European and Christian participants were	Level 3 A

(*continued on next page*)

Table 1 (*continued*)

Author (s)	Purpose	Design/method	Sample description	Variables being studied	Results/findings	Level of evidence quality rating
					more likely to obtain the vaccine than Non-White/European or Non-Christian participants, χ^2 (2, N D 774) D 12.26, $p < .01$, and χ^2 (2, N D 774) D 10.70, ($p < .01$), respectively. (6) No significant differences related to education and income level.	
Moss, Reiter, Rimer, & Brewer, 2016	Compared patient-driven and provider-driven communication relationship to HPV vaccine uptake	Secondary analysis of 2010 National Immunization Survey-Teen (NIS-T)	9021 parents or guardians of 13 to 17 year old adolescents	Communication method (1) Informed, (2) Shared (3) Efficient relationship to HPV vaccine uptake.\	(1) Provider recommendations were associated with increased odds of vaccination (all $p < .001$). (2) Provider-driven communication styles associated with higher rates of uptake of HPV vaccine (efficient style: 90% vs. shared style: 70% vs. informed style: 33%; $p < .05$ for all comparisons).	Level 3 A

only 36% were high quality. When compared to HPV vaccine initiation, they found that high quality recommendations were associated with an increase in vaccination initiation. When no provider recommendation was made there was a 23% uptake versus 74% uptake, with high quality recommendation, [OR = 9.31, 95% CI, 7.10–12.22] (Gilkey et al., 2016).

Krakow et al. (2017), studied provider recommendations relationship to HPV vaccination uptake. The participants included parents of both male and female adolescents. Two-thirds of the participants received a provider recommendation for their child to receive the HPV vaccine. There was a large discrepancy between males and females in the provider recommendations, 74.3% females compared to only 53.7% of males were provided a recommendation (Krakow et al., 2017).

Participants in the 2010 National Immunization Survey were invited to complete the Parental Attitudes Module to measure the parent's attitudes, beliefs, and experiences with adolescent vaccines. The survey also included the method of provider communication about the recommended vaccines. The sample included 9194 responses that were correlated with vaccine uptake compared to type of provider communication. The announcement technique type of recommendation was positively correlated with increased HPV vaccination uptake, while information only technique had the lowest uptake of vaccination (Moss et al., 2016). Brewer et al. (2017) found increases in HPV vaccination uptake with patients receiving announcement technique versus those in control group clinics (5.4% difference, 95% CI, 1.1%–9.7%). Using a stratified analysis they found an increase for females to be 4.6% and in males to be 6.2% for announcement technique (Brewer et al., 2017).

Cross-sectional survey data were obtained by Bruno et al. (2014) from primary care providers in an urban area. Seventy percent ($p = .92$) of the providers cited lack of preventative care visits as a barrier to recommendation for the HPV vaccine. The survey also identified that pediatric providers recommended the HPV vaccine more frequently than family practice and internist providers (66% pediatricians, 27% family practitioners, 7% internists, $p = .005$) (Bruno et al., 2014).

Alexander et al. (2015) conducted a qualitative semi-structured interview study with a convenience sample of 20 pediatricians. The study questions included knowledge, skills, and attitudes about HPV vaccination under the ACIP guidelines. They found that providers did not routinely recommend HPV vaccination due to lack of knowledge of the HPV vaccine or guidelines, lack of trust in the vaccine efficacy, discomfort discussing sexually transmitted infections with younger population groups, and discomfort discussing sexual orientation with 11 to 16 year old patients (Alexander et al., 2015). A qualitative study by Kasting et al. (2016) found that only 50% of the providers were knowledgeable about the new 9-valent HPV vaccine and changes to the ACIP recommendations (Kasting et al., 2016).

Text Message Reminders

Ahlers-Schmidt et al. (2011) surveyed 200 English speaking parents in the Midwest United States to determine preferences in communication for vaccination reminders. The participants were provided with three options for text message reminders. Parents preferred to receive some information through text messaging but only what vaccination was needed. When the group results were compared using ethnicity, the Hispanic respondents preferred more information through text message than the non-Hispanics ($\chi^2(2) = 6.36$, $p = .042$) (Ahlers-Schmidt et al., 2011). The majority of parents (80%) wanted to know the immunization needed, the child's name, and the provider contact information to schedule the appointment. Text messaging was found to be an effective reminder method as long as it can be within the 160 character limits set by some phone providers (Ahlers-Schmidt et al., 2011).

A randomized control trial was conducted looking at types of text message reminders and vaccine uptake in those with chronic medical conditions. Most of the parents in the study had unlimited texting plans (87.6%). The messages ranged from plain text reminders that an appointment needed to be scheduled, to messages containing additional educational information with the reminder. The educational messages had options to select for more education information if the parent desired. Plain messages had a higher effect on vaccination uptake than the educational text messages (10.9% vs. 41.3%; aRR 0.21, 95% CI 0.07–0.60) (Hofstetter et al., 2017).

Patel et al. (2014) conducted a prospective cluster randomized study with 10 reproductive health centers in seven states. The study implemented an automated reminder system to notify participants that their next HPV vaccination dose was due to be scheduled. Participants were able to select method of reminder at the start of the study. The options included email, phone call, text message, or Facebook message.

Table 2
Text message reminders.

Author (s)	Purpose	Design/method	Sample description	Variables being studied	Results/findings	Level of evidence quality rating
Hofstetter, Barrett, Camargo, Rosenthal, & Stockwell, 2017	Compared the effect of plain vs. educational text message reminders on receipt of needed vaccines among adolescents with chronic medical conditions	Randomized control clinical trial	295 parents of chronic medical condition (CMC) adolescents ages 11–18, 59.3% Spanish-speaking; 77.6% had adolescents with CMCs who were 13–17 years 92.5% were publicly insured	(1) Plain verses (2) Educational text messages as reminders for HPV vaccination, and association with HPV vaccine uptake	(1) Plain text messages more effective than educational text messages in short term (20% uptake with plain message, compared to 8% educational message) (2) However significant difference decreased over time (59% uptake with plain message compared to 45% with educational message, $p = .20$).	Level 1 A
Patel et al., 2014	Evaluated if reminder system increased on time completion of the HPV vaccination series	Prospective cluster randomized control trial	Ten reproductive centers in US, involving 365 females ages 19–26	Automated reminder system for next HPV vaccine dose	(1) Automated reminders did not increase HPV vaccine uptake in females ages 19–26 years. (2) HPV vaccine uptake in reminder group 17.2%, compared to 18.9% in control group ($p = .881$)	Level 1 A
Rand, Vincelli, Goldstein, Blumkin, & Szilagyi, 2017	Evaluated for differences in reminder method and HPV vaccination series completion	Parallel (2 parallel, 2 arm) randomized control trial	Urban primary care clinics, parents of adolescents ages 11–17 years, 358 in phone reminder group and 391 in text message reminder group	Comparing (1) Text message reminder and (2) phone reminder	(1) 18% increase in text message reminder group (2) only 8% increase in phone reminder compared to control groups.	Level 1 A

The study included 365 female participants between the ages of 19 and 26 years. The control group included 185 and the intervention group included 180. The control group received usual care. The text message reminder group (by self-selection) included 50% of the intervention group. The study found that message reminders in any method did not affect HPV vaccination uptake ($p = .881$) in this population group (Patel et al., 2014).

Rand et al. (2017) conducted a parallel randomized control trial with 749 parents of 11 to 17 year old adolescents in three urban primary care clinics. The participants were assigned to either phone or text reminder groups using the participant preferred method of reminder. These groups were further divided into intervention and control groups within the reminder type. There was an 18% increase in the text message reminder group but only an 8% increase in the phone reminder group compared to the control groups (49% vs. 31% with 3 doses, $p < .001$) (Rand et al., 2017).

Multi-Method Interventions

McLean et al. (2017) conducted a system based multi-method intervention within a large health system. The study included three interventions: (a) provider specific data on vaccination rates to individual providers, (b) standardized orders that staff could implement per protocol, and (c) reminder systems for the parents to schedule and keep vaccination appointments. The intervention group demonstrated a significant increase in HPV vaccination with the multi-method interventions (40.6% pre intervention to 59.3% post-intervention, $p = .0002$) compared to the control group (31.9% to 44.5%, $p = .0002$) receiving usual care (McLean et al., 2017).

A multivariable logistic regression study controlling for clustering by practice setting was conducted by Perkins et al. (2015). The study included 3961 females and 6910 males who had never received the HPV vaccine. The participants were within a single network of inner city health center clinics. Two of the eight clinics served as the intervention groups with the remaining six serving as the control groups. The study included four interventions: (a) repeated contacts with the clinic providers and staff providing education, (b) support to make practice wide changes, (c) individualized feedback on vaccination rates for the providers, and (d) incentives in the form of board certification maintenance requirements. The education component included information on the HPV vaccine safety and efficacy, and the morbidity and mortality of HPV related infections for the clinic providers (Perkins et al., 2015). Results demonstrated that provider focused interventions significantly increased the HPV vaccination rates (girls OR 1.6, boys OR 11; $p < .001$ for both) and that the improvements were sustained (girls OR 1.6, boys OR 25; $p < .05$ for both) in the intervention groups (Perkins et al., 2015).

A mixed method study within a large Federally Qualified Health Center (FQHC) group of clinics studied 38,277 participants ages 9–18 years. The study explored the patient, health care team and clinic level factors related to HPV vaccination. Qualitative interviews were completed with clinic staff and providers in four clinics, (two with high HPV vaccination rates and two with low HPV vaccination rates). The themes from the qualitative data review identified that multi-method interventions were most effective in increasing the HPV vaccine rates. Using a team approach and high quality provider recommendations were positively associated with higher completion rates (Chuang et al., 2017).

Another study compared single method with multi-method interventions. A reminder system was utilized for the single method intervention. The multi-method intervention included: (a) EHR alert reminders for the providers, (b) education to the provider and staff on vaccination rates and current guidelines, and (c) provider level feedback on HPV vaccination rates. This randomized control trial included 22,486 females ages 11 to 17 years. The multi-method interventions were significantly more effective in increasing both the uptake ($p = .001$) and completion rates ($p = .008$) for the HPV vaccine series (Fiks et al., 2013).

Discussion

The United States falls far short of the Healthy People 2020 HPV vaccination benchmark and consistently performs well below the goal vaccination rates (Centers for Disease Control and Prevention, 2017; Lu et al., 2015). There is a need to prioritize improvements on this standard of care, to decrease long-term health care costs and improve health outcomes. Nationwide, adolescents are at an increased risk for exposure to HPV through high-risk sexual behaviors. Adolescents have consistently been identified as practicing high-risk behaviors related to sexual activity. Although many parents do not believe their child is sexually active, the YRBSS data provide evidence that many are not only actively participating in high risk sexual behaviors, but are doing so before the age of 13 years (Center for Disease Control and Prevention, 2016). To provide

Table 3
Multi-method interventions.

Author (s)	Purpose	Design/method	Sample description	Variables being studied	Results/findings	Level of evidence quality rating
Cassidy, Braxter, Charron-Prochownik, & Schlenk, 2014	Examined educational intervention combined with telephone reminder to increase HPV vaccination rates in one clinic	Quasi-experimental design using health belief model.	53 parents of 11–12 year old females, 24 in intervention group, 29 in usual care control group	(1) Provider and staff education (2) Educational brochure for parents. (3) Telephone reminders	(1) Intervention group was 9.4 times more likely to initiate HPV vaccination. (2) Intervention group was 22.5 times more likely to complete HPV vaccine series	Level 2 B
Chuang et al., 2017	Examined Provider and clinic level factors affecting HPV vaccine uptake	Mixed method, logistical regression with quantitative, purposive sampling with qualitative	Large FQHC (37 clinics), 38,277 patients ages 9–18 years	(1) HPV vaccine uptake and completion rates. (2) Semi structured interviews using a standardized interview guide with 4 clinics (2 high and 2 low performing) measuring perceptions, characteristics, priorities, KSA's and beliefs	(1) HPV vaccine uptake and completion rates varied across the FQHC's. (2) Higher performing clinics shared characteristics of vaccine champion, a team approach, strong provider and support staff recommendations. (3) Tracking mechanisms and reminder systems helpful but insufficient in impact without the supportive mechanisms of the clinic team approach.	Level 3 A
Fiks et al., 2013	Examined effectiveness of automated decision support to families, providers, or combination of both	Cluster randomized trial multi-method intervention study	22,486 females ages 11 to 17 years due for HPV vaccination dose (dose #1, 2, or 3) in 22 primary care practice clinics	Four groups, 3 intervention, and 1 control group receiving standard of care. (1) Family-focused telephone reminder and links to reliable internet information on adolescent vaccines (2) Provider-focused education on guidelines and adolescent vaccines, EHR alerts, and audit feedback on HPV vaccine rates (3) Combined family-focused and provider-focused interventions. (4) Standard care	(1)Increases in vaccine uptake and completion observed with all intervention groups. (2) Combined intervention group significantly higher for both outcome measures ($p = .001$ for uptake, $p = .008$ for completion). (3) Rates for initiation were 25% in combined group compared to 18% in family focused group. (4) Completion rates were 73% in combined group compared to 64% in provider focused group.	Level 1 A
McLean et al., 2017	Evaluation of a multi component intervention to improve HPV vaccine utilization	Multi-method interventional study	Large health system, 43 clinics serving 24,658 adolescents 11–17 years	(1) Vaccination rate report to providers (2) Standardized orders (3) Reminder systems	(1) Significant increase in HPV uptakes compared to control group receiving usual care. (2) Intervention group demonstrated an 18.7% increase in HPV vaccination initiation compared to control group 12.6% in control group in ages 11–12 years. (3) There was no difference in series completion between the intervention and control groups.	Level 2 A
Perkins et al., 2015	Multi component Performance Improvement CME intervention to improve HPV vaccination rates	Multivariable logistic regression controlling for clustering by practice	3961 girls and 6910 boys who had never received HPV vaccination. Two of eight community health centers within a single network of inner-city neighborhood health centers were recruited as intervention practices and the remainder served as controls.	(1) Repeated contacts to establish trust and accountability while supporting providers to make practice-wide changes (2) Focused education on the morbidity and mortality from HPV, vaccine safety, and vaccine efficacy (3) Individualized feedback of vaccination rates and opportunity for discussion on why rates differed between providers	(1) Females at intervention practices more likely to complete the next needed HPV vaccination dose than those at control practices (OR 1.4 95% CI 1.0–2.0; post-period 1.6, 95% CI 1.1–2.2 $p < .05$ for both). (2) Males at intervention practices were also more likely to complete the next needed HPV vaccination than those at control practices (transition period OR 20, 95%	Level 3 A

Table 3 (*continued*)

Author (s)	Purpose	Design/method	Sample description	Variables being studied	Results/findings	Level of evidence quality rating
				(4) quality improvement incentives in the form of maintenance of board certification requirements to motivate demonstrable behavior change	CI 12–34; active period OR 23, 95% CI 15–37; post period OR 25, 95% CI 15–40).	

the best protection, the adolescent population needs to be fully vaccinated prior to being exposed to sexual activity. Other high-risk population groups are unvaccinated or under vaccinated. Men have been found to have a high prevalence of HPV in their oral secretions (D'Souza et al., 2014). This raises the HPV transmission risks for both females and males who practice oral sexual activities. Oral sexual behaviors have also been associated with higher levels of HPV prevalence (D'Souza et al., 2014). Older female adolescents and male adolescents have lower HPV vaccination uptake placing them at higher risk as they become more active sexually and as their number of partners increase over time. Additional concern is the lower vaccination rates in male adolescents who are sexually active with males. This review examined available evidence of effective strategies to increase HPV vaccination uptake. The review focused on three strategies to evaluate for best practice. These strategies included provider recommendations, reminder systems, and multimethod intervention models.

Provider Specific Strategies

Providers need to be aware of the complex issues involved with this cancer prevention strategy to effect change in their practice settings. Common barriers to HPV vaccination identified in the literature include lack of knowledge for the need to vaccinate, parental concerns, costs of the vaccinations, and missed opportunities. Effective strategies to overcome these barriers include education of the parents including providing reliable health information resources, education of the providers on the ACIP guidelines and HPV vaccine efficacy, and options to decrease the costs involved for both the parents and the providers (Farmar et al., 2016; Krawczyk et al., 2015). The recent updates to ACIP recommendations for adolescent males to vaccinate may not have been disseminated fully to providers. Additionally, males may have less preventative care visits during the later adolescent years, when females may be seeking options for birth control.

An often-cited rationale for vaccine refusal by parents is a fear of sexual disinhibition once the adolescent is fully vaccinated. Evidence strongly refutes that fear; instead, findings support increased understanding of the prevention of sexually transmitted infections in those vaccinated for HPV (Zimet et al., 2013). Parents are also often misinformed on vaccine safety from unreliable internet resources. Correcting this misinformation with educational interventions and redirection to reliable health information sources would have the most direct influence on parental decision making (Grandahl et al., 2017; Krawczyk et al., 2015). Utilizing anticipatory guidance earlier in the process may help decrease the misinformation exposure to the parent.

Providers need to understand the populations at highest risk for refusal include those with higher incomes, non-Hispanic and non-Black ethnicity, those with higher levels of education, and those who are not covered under the VFC programs. Providers also need to be alert to other negative health behaviors as predictors for lower levels of HPV vaccination uptake (Donadiki et al., 2014). Focusing specific efforts in those populations would have a more direct impact on increasing overall vaccination rates. There is a discrepancy in recommendations from providers, with few including the male population in the recommendation despite the ACIP guidelines (Alexander et al., 2015; Bhatta & Phillips, 2015; Krakow et al., 2017). Family practice providers also have a much lower rate of recommendations for the HPV vaccination when compared to pediatric practices (Brewer et al., 2017; Bruno et al., 2014).

Providers need to continue to offer recommendations at every contact with the adolescent population, as many who delay will eventually accept vaccination at a later visit (Gilkey, Calo, Marciniak, & Brewer, 2017). Communication between the provider and parent can result in behavior changes from anticipated regret. While this method is found to be effective with parents of male adolescents, it is not effective in parents with female adolescents (Bruno et al., 2014; Christy et al., 2016; Krawczyk et al., 2015). Using announcement communication technique has been found to be the most effective communication method to increase HPV vaccination uptake. To increase HPV vaccination rates, all providers need to utilize high quality recommendations (Brewer et al., 2017; Bruno et al., 2014; Farmar et al., 2016; Gilkey & McRee, 2016; Krakow et al., 2017; Krawczyk et al., 2015; Moss et al., 2016). While this strategy has been found to increase initial HPV vaccination uptake, it has not been found to be consistently effective in increasing completion rates of the HPV series (Moss et al., 2016).

Text Message Reminders

A majority of parents now have unlimited text message plans and prefer that method for communication of vaccine reminders (Hofstetter et al., 2017). This method has been found to be most effective if used for both scheduling the vaccination appointment and reminders to attend that appointment (Ahlers-Schmidt et al., 2011; Hofstetter et al., 2015; Hofstetter et al., 2017; Patel et al., 2014; Rand et al., 2017). While it can be an efficient reminder system method for most population groups, it is least effective in females ages 19–26 years (Patel et al., 2014). Of the studies reviewed, text message reminders are helpful to create a modest increase in completion rates for the HPV vaccine series. The increases in vaccination rates were lower when used as a single strategy compared with multi-method strategies (Ahlers-Schmidt et al., 2011; Hofstetter et al., 2017; Patel et al., 2014; Rand et al., 2017). If used with other interventions, text message reminders have shown great promise as an effective strategy to increase HPV vaccination uptake (Francis et al., 2017; Rand et al., 2017).

Multi-Method Interventions

Provider recommendation and reminder systems can be effective in raising the HPV vaccination rates. The evidence from multi-method interventions however show much higher rates of increasing the HPV vaccination rates (Cassidy et al., 2014; Chuang et al., 2017; Fiks et al., 2013; McLean et al., 2017; Perkins et al., 2015). Combining high quality provider recommendation with clinic practice changes have the potential to increase HPV vaccination rates to the goal set by Healthy People 2020 (Cassidy et al., 2014; Chuang et al., 2017; Fiks et al., 2013; Jarrett, Wilson, O'Leary, Eckersberger, & Larson, 2015; McLean et al., 2017; Office of Disease Prevention and Health Promotion, 2017; Perkins et al., 2015). The available evidence demonstrates forming a team

approach, utilizing technology to implement reminder systems, and practicing announcement technique for high quality recommendations at all visits as a cost effective approach to this preventative care vaccine (Chuang et al., 2017; Fiks et al., 2013; McLean et al., 2017; Oliver, Frawley, & Garland, 2016; Perkins et al., 2015). The evidence suggests that the most effective strategy to sustain increases in completion rates of the HPV vaccine series is multi-method where providers utilize the announcement technique, same day vaccination, and bundling of adolescent vaccinations (Cassidy et al., 2014; Chuang et al., 2017; Fiks et al., 2013; McLean et al., 2017; Perkins et al., 2015).

Implications for Practice

In all studies reviewed, sustaining a change in HPV vaccination is a challenge. This review identified the most effective strategy for increasing the uptake of HPV vaccination and for sustaining that increase over time is multi-method interventions. Provider focused interventions also demonstrated a higher level of sustained change (Perkins et al., 2015). Combining parent education, high quality provider recommendations, recall and reminder systems, and standard order protocols for HPV vaccination have been found to be most effective. Other interventions showing promise are bundling the vaccine with other adolescent vaccinations and decreasing missed opportunities. Education on HPV infection and vaccination provided to health care professionals varies across the U.S. There is a need to incorporate a focus on effective methods to increase vaccination acceptance, including high quality recommendation communication strategies at all levels of health profession education (Kornides, Garrell, & Gilkey, 2017).

Implications for Research

Further research needs to study which multi-method interventions are most effective in sustaining increased rates for HPV vaccination. Current technology provides the possibility for centralized text messages using a state level database. Studies on this reminder method compared to provider level reminder systems should be further evaluated for cost benefit. Cost benefit studies would also be helpful in identification of a balanced interventional strategy that not only achieves the desired outcomes, but also does so at the least amount of cost. Future studies should also be targeted at nurse-driven protocols such as clinical decision tools within the EHR to determine effectiveness of that strategy alone and in combination with other methods. Additionally, there is a need to compare interventions utilized in the U.S. with other countries, such as Australia and the United Kingdom, to evaluate if their interventions are more effective or if differences in healthcare coverage benefits result in their improved HPV vaccination rates. One barrier to HPV vaccination is the lack of preventive care visits in the adolescent age groups. Research exploring strategies to increase rates of wellness visits in this population group may have an indirect impact on increasing the HPV vaccination uptake, through decreasing missed opportunities. In addition, there are limited studies in non-Hispanic, non-Black, higher educated, and higher income population groups. Further research is needed to identify effective strategies to increase vaccination in those groups.

Limitations

This integrative review has some limitations. The review was conducted by a single author, which may limit interrater reliability, although the Whittemore and Knafl systematic methodology was followed (Whittemore & Knafl, 2005). The authors search terms may have missed relevant studies in the literature. The literature search also did not include grey literature or unpublished work, which may have provided additional evidence. Additionally, collaboration with a research librarian may have yielded additional studies for review not identified by the author. The review was limited to studies completed within the United States in effort to eliminate extraneous variables of access to healthcare, health care coverage differences, and systems processes that may have influence on the HPV vaccination uptake rates. This may limit identification of effective strategies that other countries have implemented.

Conclusions

Increasing vaccination rates for HPV should be a priority for all healthcare providers who work with adolescents. The burden of cost in economic numbers and quality of life indicators show that HPV infection has longitudinal effects. Through effective interventions to increase HPV vaccine uptake to follow the ACIP recommendations, providers are in a key position to create major impact in this area of healthcare. Vaccination rates have decreased overall during the last decade, and there is an urgency to change this pattern to improve outcomes for vaccine preventable diseases. Providers need to recognize their potential to create change through effective recommendations using announcement technique. Using a multi-method approach to the problem will also increase vaccination uptake in HPV vaccination series. Collaborating with parents and the healthcare team, providers can provide patient-centered health promotion care that will decrease risks of cancer in the future.

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