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Review Article

Factors associated with adolescent HPV vaccination in the U.S.: A systematic review of reviews and multilevel framework to inform intervention development

Serena A. Rodriguez[a,*], Patricia Dolan Mullen[b], Diana M. Lopez[c], Lara S. Savas[b], Maria E. Fernández (PhD)[b]

[a] Department of Population and Data Sciences, University of Texas Southwestern Medical Center, Dallas, TX, United States
[b] Center for Health Promotion and Prevention Research, The University of Texas Health Science Center at Houston School of Public Health, Houston, TX, United States
[c] MD Anderson Cancer Center, Houston, TX, United States

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ABSTRACT

Multilevel factors impact HPV vaccine series initiation and completion among adolescents in the U.S. Synthesis of these factors is needed to inform intervention development and to direct future research. Current frameworks synthesizing factors focus on females only and do not include both series initiation and completion outcomes. We conducted a systematic review of reviews to identify modifiable individual-, provider-, and clinic-level factors associated with HPV vaccination outcomes among U.S. adolescents and developed a multilevel framework illustrating relations between factors to inform intervention development. We searched Medline, PsychInfo, Pubmed, CINAHL, and ERIC databases and included reviews published 2006 to July 2, 2018 describing individual-, provider-, or clinic-level factors quantitatively associated with HPV vaccination among U.S. adolescents. Two coders independently screened reviews, extracted data, and determined quality ratings. Sixteen reviews containing 481 unique primary studies met criteria. Factors synthesized into the multilevel framework included parent psychosocial factors (knowledge, beliefs, outcome expectations, intentions) and behaviors, provider recommendation, and patient-targeted and provider-targeted clinic systems. The scope of our framework and review advances research in two key ways. First, the framework illustrates salient modifiable factors at multiple levels on which to intervene to increase HPV vaccination. Second, the review identified critical gaps in the literature at each level. Future research should link the body of literature on parental intentions to vaccination outcomes, identify provider psychosocial factors associated with recommendation behaviors and subsequent vaccine uptake in their patient population, and understand clinic factors associated with successful implementation of patient- and provider-targeted system-level interventions.

1. Introduction

The human papillomavirus (HPV) vaccine protects against oncogenic types of HPV that can lead to cancer and genital warts (Garland et al., 2007; Paavonen et al., 2007). HPV-related cancers include cervical, anal, vaginal, vulvar, penile, and oropharyngeal cancers, with the most common being cervical cancer among women and oropharyngeal cancers among men (Viens et al., 2016). The CDC Advisory Committee for Immunization Practices (ACIP) recommends the HPV vaccine be administered to adolescents aged 1112 years, although it is available for adolescents starting at age nine and adults up to age 45 (Meites et al., 2016; Meites et al., 2019). Current HPV vaccination coverage lags behind the Health People 2020 national goal that 80% of 13–15 year olds complete the multi-dose series (U.S. Department of Health and Human Services Office of Disease Prevention and Health Promotion, n.d.; Walker et al., 2019). National data show HPV vaccine initiation rates of 70% of females and 66% of males aged 13–17 years, and 54% of females and 49% of males aged 13–17 years are considered up to date on all doses (Walker et al., 2019).

To increase vaccination, it is important to understand the diverse multilevel factors associated with HPV vaccine series initiation and completion. Synthesizing these factors in a multilevel framework that illustrates their associations can inform future interventions aiming to increase HPV vaccination coverage. The National Cancer Institute (NCI)

* Corresponding author at: Department of Population and Data Sciences, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390, United States.
E-mail address: Serena.Rodriguez@UTSouthwestern.edu (S.A. Rodriguez).

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specifically calls for multilevel interventions across the cancer control continuum (National Cancer Institute, 2012). However, current frameworks and evidence syntheses of factors associated with HPV vaccination are limited in their scope, outcomes, and populations (Batista Ferrer et al., 2014; Batista Ferrer et al., 2015; Brewer and Fazekas, 2007; Fernández et al., 2010; Katz et al., 2010). Fernandez and colleagues were the first to develop a multilevel logic model illustrating the relations between parental-, provider-, clinic-, community-, and policy-level factors associated with HPV vaccination acceptance and willingness to vaccinate (Fernández et al., 2010). That model, however, has limited applicability to inform interventions focused on vaccine series initiation and completion. Although more recent frameworks illustrate relations between multilevel factors associated with behavioral outcomes, they were produced before the vaccine was recommended for males (Batista Ferrer et al., 2014; Katz et al., 2010; Tiro et al., 2012).

An updated framework integrating multilevel factors associated with HPV vaccine series initiation and completion for male and female adolescents in the U.S. is needed. Therefore, our systematic review or reviews consolidates the large body of literature describing multilevel factors associated with HPV vaccination outcomes among U.S. adolescents aged 11–17 years, and we illustrate the relations among these factors in an empirically-based and theoretically-informed multilevel framework. We limit the scope of our review and framework to the individual-, provider-, and clinic-levels and do not include population levels such as the community or policy levels. While policies such as mandatory HPV vaccination for school entry have been successful at increasing coverage, particularly outside of the U.S., states are slow to adopt such policies which often have limited support (Barraza et al., 2016; Brandt et al., 2016; Calo et al., 2016; Vercruysse et al., 2016). Instead, we focus on the individual-, provider-, and clinic-levels to inform the development of interventions targeting vaccination decision makers (parents and adolescents), vaccine administerers (providers), and clinic systems.

2. Methods

Methods are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist (Moher et al., 2009).

2.1. Eligibility criteria

We included English-language peer-reviewed reviews (defined as comprehensive, integrated, or systematic literature reviews or meta-analyses) published between 2006, when the U.S. Food and Drug Administration approved the first available HPV vaccine, (U.S. Food and Drug Administration, 2006) through the date of the final search (July 2, 2018). Those reporting modifiable correlates or predictors (factors) of HPV vaccine initiation and/or completion for U.S. adolescents ages 9–17 years via parental reports or electronic health records were eligible. We defined modifiable factors as those that have the potential to change through intervention including psychosocial, attitudinal, or behavioral variables at the individual- and provider-levels and procedural or systems variables at the clinic-level. We excluded the following: reviews with only HPV vaccine awareness, acceptability, and intention outcomes; commentaries, editorials, dissertations, abstracts, and conference proceedings; and reviews with only qualitative primary studies. However, reviews were included if they contained findings based on mixed methods research or if qualitative data were presented with quantitative data corroborating findings.

2.2. Information sources and search

We searched Pubmed (NLM), Medline and PsychInfo (Ovid), and CINAHL and ERIC (Ebsco). A health sciences librarian experienced in developing and documenting search strategies for systematic reviews assisted in developing the search strategy in Medline (see Supplemental Materials). Concepts in the search included: human papillomavirus, immunizations or vaccination, parents or guardians, and adolescents. The search was adapted for use in PsychInfo, Pubmed, CINAHL, and ERIC databases.

2.3. Study selection and data collection

Two reviewers used standardized forms to conduct title and abstract screening, full text reviews, and data extraction. First, the reviewers (blind to journal titles, authors, and author affiliations) independently screened titles and abstracts against eligibility criteria. We calculated interrater reliability based on a random sample of $n = 65$ articles ($\kappa = 0.85$). Next, reviewers assessed the full text of reviews considered for inclusion after title and abstract screening to determine final eligibility. After full text reviews, one reviewer searched reference lists of the final included reviews for additional records. Reviewers discussed all discrepancies during study selection and data collection to develop consensus.

The reviewers independently extracted review characteristics (aims, search period, eligibility criteria) and modifiable individual-, provider-, and clinic-level correlates and predictors (factors) of HPV vaccination initiation and completion. For reviews including multiple countries, reviewers extracted data associated with adolescents in the U.S. only. Reviewers extracted factors presented by authors in tables and/or text as associated with vaccination outcomes and supported by ≥ 2 quantitative primary studies. When a review labeled an outcome as "uptake," we interpreted this as initiation only unless the authors explicitly stated they also assessed completion. For each review, modifiable factors were organized in a grid by positive or negative association with vaccination initiation or completion, adolescent sex when specified, and level (individual-, provider-, or clinic-level). Reviewers also coded factors with mixed or null results. For consistency, reviewers relabeled psychosocial factors that were similar (e.g., perceived risk and perceived susceptibility) where appropriate.

For systematic reviews, reviewers used the AMSTAR checklist to describe quality. AMSTAR is an 11-item validated tool used to assess methodological rigor of systematic reviews (Shea et al., 2007; Shea et al., 2009). Example items include: 1) was an "a priori" design provided, 2) was there duplicate study selection and data extraction, and 3) was the scientific quality of the included studies assessed and documented? Item response options included "yes," "no," "can't answer," and "not applicable." We removed two items post hoc: 1) "were the methods used to combine the findings of the studies appropriate," and 2) "was the likelihood of publication bias assessed?" Both required meta-analytic techniques, and no reviews included meta-analyses. Guidance on AMSTAR scoring for reviews without meta-analyses is to not calculate an overall score (Pieper et al., 2018). Therefore, we present counts for each response option in the results.

During data collection and synthesis, we chose not to weigh findings from some reviews over others for two reasons. First, our eligibility criteria included multiple types of reviews (integrated reviews, systematic reviews, comprehensive literature reviews) with varying methodologies to capture a robust sample of studies. There is no objective measure to assess the quality of multiple types of reviews against one another, and AMSTAR response option counts for systematic reviews are for descriptive purposes only. Second, factors associated with vaccination outcomes were consistent across review types and primary studies included in the reviews. We therefore describe factors associated with vaccination outcomes from all of the reviews.

3. Results

3.1. Study selection

We identified 356 unique records from the database search and 10

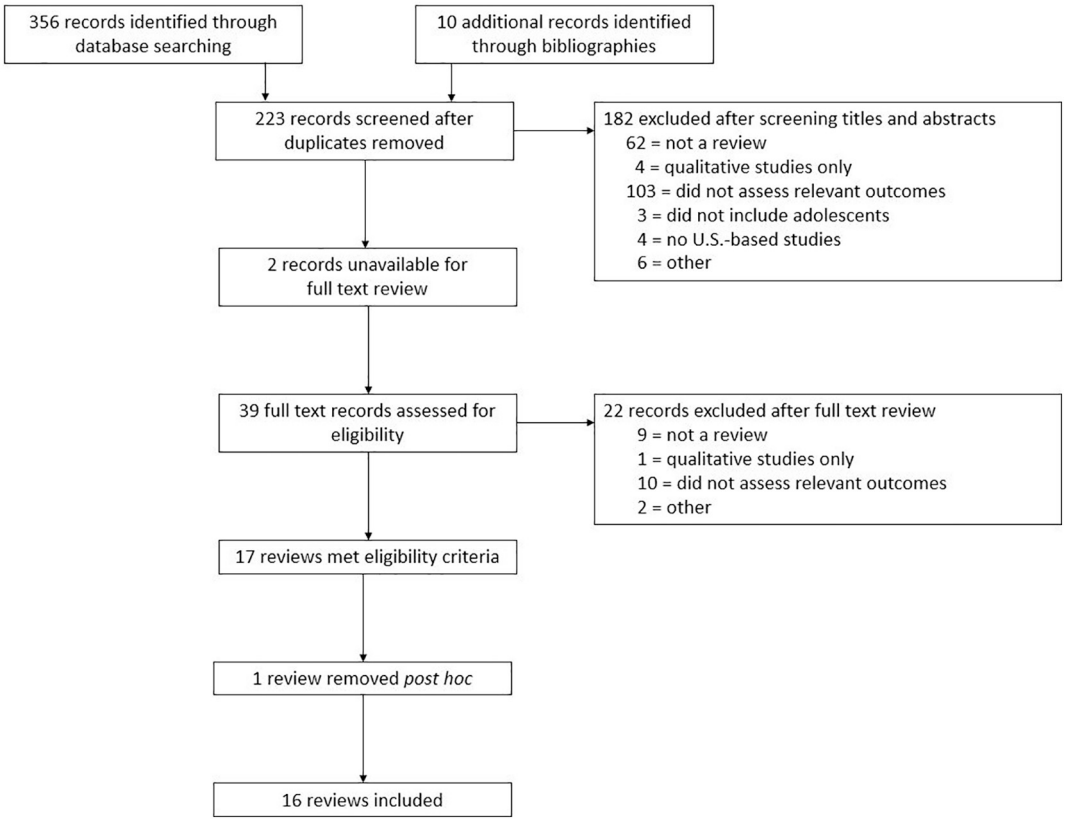


Fig. 1. PRISMA flowchart.

additional records from reference lists. Seventeen met inclusion criteria after the two-step screening process (Fig. 1). Principal reasons for exclusion were not being a review and not assessing HPV vaccination outcomes. One meta-analysis was excluded post hoc because it included only demographic correlates of vaccination outcomes (Fisher et al., 2013). (Excluded citations are available from corresponding author.)

3.2. Characteristics of reviews

Most reviews ($n = 11$) included were systematic literature reviews ($n = 2$ integrative reviews; $n = 3$ literature reviews) (Gallagher et al., 2016; Holman et al., 2014; Kessels et al., 2012; Kim and LeClaire, 2017; Loke et al., 2017; Niccolai and Hansen, 2015; Radisic et al., 2016; Rosen et al., 2018; Ryan et al., 2018; Trim et al., 2012; Walling et al., 2016). None included meta-analyses of modifiable factors associated with adolescent HPV vaccination (Table 1). Among the systematic reviews, all but one (Holman et al., 2014) conducted comprehensive literature searches (defined as listing at least two search sources and one supplemental search strategy) and provided characteristics of all studies included. No systematic reviews listed potential conflicts of interest for included studies, and none included a list of excluded studies. Responses for all other AMSTAR items varied. (AMSTAR checklist for all reviews available from corresponding author.)

Five reviews examined outcomes among females only, (Bartlett and Peterson, 2011; Galbraith et al., 2016; Kessels et al., 2012; Small et al., 2014; Valentino and Poronsky, 2016) one among males, (Radisic et al., 2016) and ten among males and females (Gallagher et al., 2016; Holman et al., 2014; Kim and LeClaire, 2017; Loke et al., 2017; Niccolai and Hansen, 2015; Rosen et al., 2018; Ryan et al., 2018; Trim et al., 2012; Vollrath et al., 2018; Walling et al., 2016). Eight reviews assessed HPV vaccine uptake or initiation (Bartlett and Peterson, 2011; Loke et al., 2017; Radisic et al., 2016; Small et al., 2014; Trim et al., 2012; Valentino and Poronsky, 2016; Vollrath et al., 2018; Walling et al., 2016). One assessed series completion,(Gallagher et al., 2016) and seven reviews assessed initiation and completion (Galbraith et al., 2016; Holman et al., 2014; Kessels et al., 2012; Kim and LeClaire, 2017; Niccolai and Hansen, 2015; Rosen et al., 2018; Ryan et al., 2018). Publication dates ranged from 2011[39] to 2018 (Rosen et al., 2018; Ryan et al., 2018; Vollrath et al., 2018). Search end dates ranged from 2010[39] to March 1, 2017 (Vollrath et al., 2018). Reviews included 481 unique primary studies, with 115 (28%) primary studies included in more than one review. We were unable to retrieve complete bibliographies for two reviews (Gallagher et al., 2016; Valentino and Poronsky, 2016). (List of primary studies and citing reviews available from corresponding author.)

3.3. Factors positively associated with HPV vaccination outcomes

Parent and adolescent psychosocial factors, adolescent, parent, and provider behaviors, and clinic systems targeting providers and parents were positively associated with HPV vaccination outcomes in reviews (Table 2).

3.3.1. Parent psychosocial factors

One review identified parental acceptance of the HPV vaccine as positively associated with initiation among male and female adolescents (Loke et al., 2017); however, the review did not define how acceptance was operationalized. Parental knowledge of the HPV vaccine was positively associated with series initiation for males and females (Kim and LeClaire, 2017) and series completion for females.(Gallagher et al., 2016) Among parents needing more information about the vaccine, satisfaction with the quality of information received was positively associated with initiation among females (Kessels et al., 2012).

Parental perceived benefits of the vaccine, (Valentino and Poronsky, 2016) perceived susceptibility of child to HPV or HPV-related diseases, (Holman et al., 2014; Trim et al., 2012) perceived vaccine effectiveness,

Table 1
Review characteristics and factors assessed by HPV vaccination outcomes.

Author, year; search time period; review type	# of studies/pubs (*k*); study design	Population;[a] country[b]	Modifiable factors assessed	AMSTAR[c]
Outcome: HPV vaccine series initiation				
Loke, 2017 Jan 2016 – Mar 4, 2017 Systematic review	*k* = 42 studies Cross-sectional; data-report; retrospective cohort; prospective cohort	Parents of males and females 9–21 yrs. U.S., United Kingdom, Norway, Hong Kong, Taiwan, Malaysia, Japan, Canada, Australia, Netherlands, Germany, France, Denmark, Latvia	• *Individual:* Parental acceptance, information, parental concerns (safety, sexual activity, perceived susceptibility), peer encouragement parental preference to wait until older • *Provider:* Provider recommendation	Yes: 5 No: 4 CA: 2 NA: 0
Radisic, 2017 Oct 2009 – Jul 10, 2015 Systematic review	*k* = 18 studies Quantitative, qualitative, mixed methods	Parents of males ages 9–18 yrs. U.S., Canada, Italy, Denmark	• *Individual*: Parental attitudes towards vaccinations in general, beliefs, concerns (efficacy, safety, related to sexual activity), cues to action, cost, egalitarianism beliefs, parent-child dialogue, perceived risks and benefits, religion • *Provider*: Provider recommendation	Yes: 6 No: 3 CA: 2 NA: 0
Vollrath, 2017 Jan 1, 1999 – Mar 1, 2017 Integrative review	*k* = 37 publications Cluster randomized trial; cross-sectional; nonrandomized control trial; qualitative; pre/posttest; randomized intervention trial; retrospective chart review; systematic review	Parents of adolescent males and females U.S., Australia, Canada, Georgia, Honduras, India, Iran, Italy, Pakistan	• *Individual:* Adolescent receipt of other vaccines; Parental attitudes (perceived susceptibility, need, concerns about safety), knowledge • *Provider:* Provider recommendation • *Clinic:* Patient reminders; provider education; provider reminder/recall	NA
Walling, 2016 Jan 1, 2006 – Apr 30, 2015 Systematic review	*k* = 51 publications Intervention studies	Males and females 11–26 yrs. U.S.	• *Clinic*: Community, practice, and policy level interventions (physician-focused; reminder & recall systems; school-based programs; social marketing).	Yes: 5 No: 4 CA: 2 NA: 0
Valentino, 2016 N/A Literature review	N/A N/A	Adolescent females; young adult females; parents of adolescent females; providers U.S.	• *Individual*: Adolescents' attitudes, knowledge; Parental concerns (safety, sexual connotation), cost, knowledge, perceived risk • *Provider*: Cost, knowledge, perceived parental attitudes regarding HPV vaccination, provider recommendation, recommendation practices, time	NA
Small, 2014 Jan 1, 2009 – Jun 1, 2011 Literature review	*k* = 19 publications Longitudinal, cross-sectional	Females; parents of adolescent females; providers U.S.	• *Individual*: Parental concerns (safety), cost, HPV risk, history of preventative health care, insurance, knowledge • *Provider*: Provider recommendation • *Clinic*: Vaccine availability, vaccination opportunity in several types of health care visits	NA
Trim, 2012 2001–2011 Systematic review	*k* = 53 studies Cross-sectional	Parents of adolescents U.S., EU, Canada, Asia, New Zealand, Australia	• *Individual*: Parental attitudes towards vaccines in general and the HPV vaccine, behaviors, concerns (safety), knowledge	Yes: 2 No: 6 CA: 2 NA: 1
Bartlett, 2011 2006 – Dec 30, 2010 Literature review	*k* = 14 studies Retrospective cohort, prospective cohort, randomized retrospective cohort, mixed methods	Females ages 9–18 yrs.; providers U.S.	• *Individual*: Parental attitudes, concerns (related to sexual connotation, safety, efficacy), knowledge, need for accurate vaccine information • *Provider*: Attitudes, cost, provider recommendation • *Clinic*: Vaccine availability	NA
Outcome: vaccine series completion				
Gallagher, 2012 Database inception – Feb 2014 Systematic review	*k* = 48 studies in 61 publications No study designs mentioned; included only those reporting multivariable analyses or qualitative findings	Males and females 9–19 yrs. U.S., Canada, Europe	• *Individual*: Concomitant healthcare, healthcare utilization, risk behaviors; Parental history of preventative health care, knowledge • *Clinic*: Accessibility, delivery model (health facility, school-based, mixed-model)	Yes: 8 No: 3 CA: 0 NA: 0
Outcome: vaccine series initiation and completion				
Rosen, 2018 N/A – Aug 2016 Systematic review	*K* = 60 publications Cross-sectional; qualitative; retrospective study	Healthcare clinicians defined as an individual qualified to deliver health care services to patients within recommended age group for vaccination U.S.	• *Provider:* Provider knowledge and beliefs about HPV and HPV vaccine; attitudes and beliefs about recommending HPV vaccine; intentions to recommend HPV vaccine; professional practices regarding HPV vaccination	Yes: 3 No: 6 CA: 2 NA: 0
Ryan, 2018 1996 – Nov 2016 Systematic review	*k* = 15 publications Intervention; randomized controlled trial; qualitative focus groups; survey	Parents of adolescent males and females; women 18+ yrs.; providers U.S.	• *Individual*: Parental acceptance of HPV vaccine, attitudes, awareness, healthcare decision-making, intention, knowledge • *Provider*: Provider perspective on patients, recommendation	Yes: 3 No: 6 CA: 2 NA: 0
Kim, 2017	*k* = 22 publications	Immigrant parents of males and females age-eligible for HPV vaccine	• *Individual:* Parental awareness, concerns, knowledge, willingness, healthcare utilization	Yes: 4 No: 6

(*continued on next page*)

Table 1 (*continued*)

Author, year; search time period; review type	# of studies/pubs (*k*); study design	Population;[a] country[b]	Modifiable factors assessed	AMSTAR[c]
Jun 2006 – Feb 2015 Systematic review	Cross-sectional, intervention, mixed methods, qualitative		• *Provider:* Provider recommendation	CA: 1 NA: 0
Galbraith, 2016 Database inception – Jan 2015 Integrative review	*k* = 67 studies Cross-sectional; qualitative; mixed methods; longitudinal cohort; intervention tests	Parents of African-American and Latino adolescent females U.S.	• *Individual*: Adolescent history of preventative care; Parental acculturation, attitudes, beliefs, concerns (safety, effectiveness), cost, history of preventative health care, information source, intentions to vaccinate, knowledge, parent- daughter communication (sex-related), social norms, social support • *Provider*: Provider recommendations	NA
Niccolai, 2015 Database inception – Jul 2014 Systematic review	*k* = 14 studies Randomized controlled trials; quasi-experimental	Males and females ≤18 yrs. U.S.	• *Clinic*: Community and practice level interventions (physician-focused; reminder & recall systems; school-based programs; social marketing)	Yes: 5 No: 5 CA: 1 NA: 0
Holman, 2014 Jan 1, 2009 – Dec 31, 2012 Systematic review	*k* = 55 publications Quantitative, qualitative	Parents of adolescents 11–17 yrs.; health care professionals; under-served & disadvantaged populations; adolescent males U.S.	• *Individual*: Parental awareness, beliefs, concerns (accessibility, safety, effectiveness), cost, HPV related experiences, parent-child communication, perceived risks and benefits, religion • *Provider*: Cost, knowledge, perceived parental attitudes regarding HPV vaccination, recommendation practices	Yes: 0 No: 8 CA: 2 NA: 1
Kessels, 2012 2006 – Mar 7, 2011 Systematic review	*k* = 25 studies in 33 publications Cross-sectional, longitudinal	Females 9–18 yrs. U.S.	• *Individual*: Adolescents' healthcare utilization, information source, knowledge, vaccination history, sexual activity related factors; Parental attitudes, beliefs, knowledge, history of sexually transmitted infections or HPV related diseases, intention to vaccinate • *Provider*: Provider recommendation	Yes: 6 No: 3 CA: 2 NA: 0

[a] Extracted data related to vaccination among adolescents only.
[b] Extracted data related to HPV vaccination in the U.S. only.
[c] Assessed for systematic reviews only. CA = Can't answer; NA = Not Applicable.

(Galbraith et al., 2016; Trim et al., 2012; Valentino and Poronsky, 2016) and perceived vaccine safety (Galbraith et al., 2016) were associated with initiation among female adolescents. Perceived benefits included the prevention of cervical cancer and genital warts (Valentino and Poronsky, 2016). One review found perceived effectiveness and perceived susceptibility to be positively associated with initiation among both males and females (Trim et al., 2012). Finally, parental intentions to vaccinate were positively associated with initiation among adolescent males (Radisic et al., 2016).

3.3.2. Adolescent psychosocial factors

Only one review identified adolescent psychosocial factors positively associated with vaccination outcomes with adolescent knowledge of HPV and the HPV vaccine associated with initiation among females (Kessels et al., 2012).

3.3.3. Parent behaviors

Reviews reported multiple parent behaviors positively associated with vaccination. For females, parental seeking of HPV vaccine information and familial decision making about the vaccine was associated with initiation among those with immigrant parents (Kim and LeClaire, 2017). Maternal experience obtaining Pap tests was associated with initiation and completion (Bartlett and Peterson, 2011). For males, parents discussing the vaccine with sons was associated with initiation (Radisic et al., 2016).

3.3.4. Adolescent behaviors

Adolescent interaction with the healthcare system was positively associated with vaccination initiation among both males and females. Specifically, regular visits with a provider was associated with initiation among females, (Bartlett and Peterson, 2011) and recent visit with a provider and receipt of other adolescent vaccines were associated with initiation among males (Radisic et al., 2016; Vollrath et al., 2018) and females (Kessels et al., 2012; Small et al., 2014; Vollrath et al., 2018).

3.3.5. Provider behavior

Reviews consistently identified provider recommendation of the HPV vaccine as positively associated with vaccination outcomes. Seven reviews found a positive association between a provider recommendation and series initiation (Bartlett and Peterson, 2011; Galbraith et al., 2016; Holman et al., 2014; Small et al., 2014; Valentino and Poronsky, 2016) and completion (Gallagher et al., 2016; Kessels et al., 2012) among females. Four reviews described the positive association between a provider recommendation and series initiation among both males and females (Kim and LeClaire, 2017; Loke et al., 2017; Ryan et al., 2018; Vollrath et al., 2018).

3.3.6. Clinic systems

Provider-targeted systems and patient-targeted reminder/recall systems were positively associated with vaccination outcomes among males and females. Specifically, provider assessment and feedback and reminder/recall systems were associated with initiation and completion (Rosen et al., 2018; Vollrath et al., 2018; Walling et al., 2016). Provider education paired with additional provider-targeted systems, and reminder/recall paired with additional provider-targeted systems were associated with initiation only (Ryan et al., 2018; Vollrath et al., 2018). Patient reminder/recall systems were associated with both initiation and completion among males and females (Niccolai and Hansen, 2015;

Table 2
Factors positively associated with HPV vaccination outcomes among U.S. female and male adolescents ages 9–17 years.

Target population	Outcomes		
	Initiation	Completion	Initiation and completion
Female adolescents	*Parent psychosocial factors* Knowledge • HPV[a] (Galbraith et al., 2016; Kessels et al., 2012; Small et al., 2014) • HPV vaccine[a] (Small et al., 2014) Beliefs • Perceived benefits (Valentino and Poronsky, 2016) • Perceived susceptibility (Holman et al., 2014) • Perceived vaccine effectiveness (Galbraith et al., 2016; Valentino and Poronsky, 2016) • Perceived vaccine safety (Galbraith et al., 2016) Satisfaction with information (Kessels et al., 2012) *Adolescent psychosocial factors* Knowledge • HPV[25] • HPV vaccine (Kessels et al., 2012) *Parent behaviors* • Seeking HPV vaccination information (Kim and LeClaire, 2017) • Familial decision making about vaccine (Kim and LeClaire, 2017) • Maternal experience with Pap tests (Bartlett and Peterson, 2011) *Adolescent behaviors* • Interaction with healthcare system • Regular visit with provider (Bartlett and Peterson, 2011) • Recent visit with provider (Kessels et al., 2012; Small et al., 2014) • Receipt of other adolescent vaccines (Kessels et al., 2012) *Provider behavior* • Recommendation ((Holman et al., 2014); (Galbraith et al., 2016); (Valentino and Poronsky, 2016); (Small et al., 2014); (Bartlett and Peterson, 2011))	*Parent psychosocial factors* Knowledge • HPV vaccine (Gallagher et al., 2016) *Provider behavior* • Recommendation (Gallagher et al., 2016; Kessels et al., 2012) *Adolescent behaviors* • Interaction with healthcare system[a] (Gallagher et al., 2016) *Parental behaviors* • Maternal experience with Pap tests (Gallagher et al., 2016)	
Male adolescents	*Parent psychosocial factor* • Intentions to vaccinate (Radisic et al., 2016) *Parent behavior* • Discussions about vaccine with son (Radisic et al., 2016) *Adolescent behavior* • Interaction with healthcare system ••Visit with provider in past year (Radisic et al., 2016)		
Female and male adolescents	*Parent psychosocial factors* • Acceptance (Loke et al., 2017) • Knowledge •• HPV vaccine (Kim and LeClaire, 2017) • Beliefs •• Perceived effectiveness (Trim et al., 2012) •• Perceived susceptibility (Trim et al., 2012) *Adolescent behaviors* • Interaction with healthcare system •• Receipt of other adolescent vaccines (Vollrath et al., 2018) *Provider behavior* • Recommendation (Kim and LeClaire, 2017; Loke et al., 2017; Ryan et al., 2018; Vollrath et al., 2018) *Clinic systems* Provider-targeted • Assessment and feedback (Walling et al., 2016) • Education only[a],(Vollrath et al., 2018) • Education paired + other (Vollrath et al., 2018) • Reminder/recall only (Vollrath et al., 2018) • Reminder/recall + other (Ryan et al., 2018; Vollrath et al., 2018) Patient-targeted • Reminder/recall (Walling et al., 2016)		*Clinic systems* Provider-targeted • Assessment and feedback (Walling et al., 2016) • Reminder/recall only (Rosen et al., 2018) Patient-targeted • Reminder/recall (Niccolai and Hansen, 2015; Vollrath et al., 2018; Walling et al., 2016)

[a] Mixed results found for association between factor and vaccination outcomes.

Vollrath et al., 2018; Walling et al., 2016). One review noted that provider-targeted interventions were more successful in increasing series initiation, and parent-targeted reminders were more successful for series completion.(Walling et al., 2016)

3.4. Factors negatively associated with vaccination outcomes

Reviews described parent psychosocial factors, adolescent behaviors, and provider behaviors negatively associated with vaccine initiation (Table 3). No reviews described factors negatively associated with completion.

3.4.1. Parent psychosocial factors

Lack of knowledge about the HPV vaccine and requiring additional information were negatively associated with initiation for both males and females (Galbraith et al., 2016; Holman et al., 2014; Loke et al., 2017; Valentino and Poronsky, 2016; Vollrath et al., 2018). Specific examples of parental knowledge gaps included not knowing the vaccine is available for males and (Holman et al., 2014) the vaccine is a multi-dose series (Galbraith et al., 2016; Holman et al., 2014). Parental dissatisfaction with information received about the vaccine was negatively associated with initiation for females (Kessels et al., 2012).

Reviews consistently reported negative associations between parental beliefs and concerns about the HPV vaccine and vaccine series initiation. Low perceived need, (Bartlett and Peterson, 2011; Galbraith et al., 2016; Holman et al., 2014; Trim et al., 2012; Valentino and Poronsky, 2016; Vollrath et al., 2018) low perceived susceptibility of child to HPV or HPV-related diseases, (Galbraith et al., 2016; Loke et al., 2017; Ryan et al., 2018; Small et al., 2014; Valentino and Poronsky, 2016) and concerns about vaccine safety (Bartlett and Peterson, 2011; Kessels et al., 2012; Kim and LeClaire, 2017; Loke et al., 2017; Small et al., 2014; Valentino and Poronsky, 2016; Vollrath et al., 2018) were negatively associated with initiation in males and females. Reasons for not needing the vaccine were young age, (Bartlett and Peterson, 2011; Holman et al., 2014; Trim et al., 2012) being male, (Holman et al., 2014) and no sexual activity (Bartlett and Peterson, 2011; Trim et al., 2012). Examples of parental safety concerns included concerns about side effects (Bartlett and Peterson, 2011; Kessels et al., 2012; Vollrath et al., 2018) and vaccine novelty (Bartlett and Peterson, 2011; Valentino and Poronsky, 2016). Additionally, parental concerns about vaccine effectiveness were negatively associated with initiation among females, (Galbraith et al., 2016; Kim and LeClaire, 2017; Valentino and Poronsky, 2016) and low parental perceived benefits of the vaccine was negatively associated with initiation among males (Holman et al., 2014). Finally, four reviews identified parental concerns about cost of the HPV vaccine as negatively associated with initiation for males and females (Bartlett and Peterson, 2011; Holman et al., 2014; Valentino and Poronsky, 2016; Vollrath et al., 2018).

3.4.2. Parent behavior

One review identified previous parental refusal to vaccinate his/her child as negatively associated with HPV vaccine series initiation among males and females (Trim et al., 2012).

3.4.3. Adolescent behavior

One review identified lack of adolescent interaction with the healthcare system, specifically a recent preventive care visit, as negatively associated with initiation among females (Kessels et al., 2012).

3.4.4. Provider behavior

Lack of provider recommendation for the HPV vaccination was negatively associated with HPV vaccine series initiation among males (Holman et al., 2014) and females (Galbraith et al., 2016; Holman et al., 2014; Valentino and Poronsky, 2016) in three reviews.

3.5. Factors with mixed associations with vaccination outcomes

At the parent psychosocial level, reviews differed on whether parental knowledge of the HPV vaccine was associated with initiation (Small et al., 2014) and whether parental knowledge of the virus was associated with initiation and completion (Galbraith et al., 2016; Gallagher et al., 2016; Kessels et al., 2012; Small et al., 2014). Additionally, mixed associations were found between parental concerns about sexual activity and vaccination outcomes (Kim and LeClaire, 2017; Trim et al., 2012). While adolescent interaction with the healthcare system was associated with initiation among females, mixed associations were found between adolescent interaction with the healthcare system and vaccine series completion in one review (Gallagher et al., 2016). At the clinic level, although provider education paired with additional provider-targeted interventions was associated with initiation, there were mixed associations between provider education alone and vaccination outcomes (Vollrath et al., 2018).

4. Discussion

We conducted a systematic review of 16 reviews to synthesize multilevel factors associated with HPV vaccination among U.S. adolescents. The scope of the review advances research in two key ways. First, we can use the empirical evidence of modifiable factors associated with HPV vaccination and draw upon health behavior theory to develop a multilevel framework that can inform intervention development and increase HPV vaccine initiation and completion. Second, the review provides an up-to-date synthesis of salient factors associated with HPV vaccination and allows us to identify critical gaps in the literature.

4.1. Multilevel framework of HPV vaccination

Drawing upon empirical evidence from the reviews and health promotion theories, we developed a multilevel framework illustrating hypothesized causal pathways between modifiable factors associated with HPV vaccination outcomes (Fig. 2). Specifically, we drew upon Social Cognitive Theory (SCT), (Bandura, 2004) the Integrated Behavior Model (IBM), (Montano and Kasprzyk, 2015) and the Health Belief Model (HBM) (Skinner et al., 2015) to build the multilevel framework. In short, according to the SCT, behavior change is influenced by personal cognitive influences (e.g., self-efficacy, knowledge, outcome expectations), environmental influences (e.g., normative beliefs, barriers and opportunities), and supporting behavioral factors (e.g., skills, intentions, reinforcement). Intention is the most important factor related to behavior change in the IBM, and intention is informed by attitudes, perceived norms, and personal agency (Montano and Kasprzyk, 2015). Finally, in the HBM, individual beliefs such as perceived susceptibility, severity, benefits, and barriers, and self-efficacy predict individual behaviors, and the model is often applied to preventive behaviors such as vaccination or screening (Skinner et al., 2015; Tanner-Smith and Brown, 2010).

The structure of our framework is based on one developed by Green and Kreuter used for organizing needs assessment information (Green and Kreuter, 2005) and adapted by Bartholomew Eldredge and colleagues to inform multilevel intervention development (Bartholomew Eldredge et al., 2016). We chose not to develop multiple frameworks by adolescent sex since factors associated with outcomes were similar across the sexes and reviews. Additionally, we did not include or exclude factors in the framework based on the number of reviews identifying them as associated with outcomes. Instead, we relied on health promotion theories to guide decision-making. This framework is the first to use empirical evidence and theory to organize multilevel correlates and predictors of HPV vaccine series initiation and completion for both male and female adolescents in the U.S.

Both SCT (Bandura, 2004) and the IBM (Montano and Kasprzyk, 2015) highlight knowledge as an important precondition for behavior

Table 3
Factors negatively associated with HPV vaccination outcomes among U.S. female and male adolescents ages 9–17 years.

Target population	Outcome
	Initiation
Female adolescents	*Parent psychosocial factors*
	• Lack of knowledge, require information (Valentino and Poronsky, 2016) •• HPV vaccine (Galbraith et al., 2016) • Beliefs •• Low perceived need (Galbraith et al., 2016; Valentino and Poronsky, 2016) •• Low perceived susceptibility (Galbraith et al., 2016; Valentino and Poronsky, 2016) •• Concerns about vaccine safety (Bartlett and Peterson, 2011; Kessels et al., 2012; Valentino and Poronsky, 2016) •• Concerns about vaccine effectiveness (Galbraith et al., 2016; Kim and LeClaire, 2017; Valentino and Poronsky, 2016) • Concerns about cost (Bartlett and Peterson, 2011) • Concerns about sexual activity[a], (Kim and LeClaire, 2017; Trim et al., 2012) • Dissatisfaction with information on vaccine (Kessels et al., 2012)
	Adolescent behavior
	• Interaction with healthcare system •• Lack of recent preventive care visit (Kessels et al., 2012)
	Provider behavior
	• Lack of recommendation ((Galbraith et al., 2016); (Valentino and Poronsky, 2016))
Male adolescents	*Parent psychosocial factors*
	• Lack of knowledge (Holman et al., 2014) • Beliefs •• Low perceived benefit (Holman et al., 2014) •• Low perceived need (Holman et al., 2014)
	Provider behavior
	• Lack of recommendation (Holman et al., 2014)
Female and male adolescents	*Parent psychosocial factors*
	• Lack of knowledge, require information (Holman et al., 2014; Loke et al., 2017; Vollrath et al., 2018) • Beliefs •• Low perceived need (Bartlett and Peterson, 2011; Holman et al., 2014; Trim et al., 2012; Vollrath et al., 2018) •• Low perceived susceptibility (Loke et al., 2017; Ryan et al., 2018; Small et al., 2014) •• Concerns about vaccine safety (Kim and LeClaire, 2017; Loke et al., 2017; Small et al., 2014; Vollrath et al., 2018) • Concerns about cost (Holman et al., 2014; Valentino and Poronsky, 2016; Vollrath et al., 2018)
	Parent behavior
	• Previous refusal to vaccinate child (Trim et al., 2012)
	Provider behavior
	• Lack of recommendation (Holman et al., 2014)

[a] Mixed results found for association between factor and vaccination outcomes.

change. We synthesized review findings and theory to show that parents should have knowledge of HPV, the HPV vaccine, and the availability of options to pay for the vaccine (Bartlett and Peterson, 2011; Galbraith et al., 2016; Gallagher et al., 2016; Holman et al., 2014; Kessels et al., 2012; Kim and LeClaire, 2017; Loke et al., 2017; Valentino and Poronsky, 2016; Vollrath et al., 2018). Parents also need to know available options to pay for the vaccine since cost was a barrier to initiation (Bartlett and Peterson, 2011; Holman et al., 2014; Valentino and Poronsky, 2016; Vollrath et al., 2018). According to the IBM, intention to perform a behavior is a significant predictor of the behavior, (Montano and Kasprzyk, 2015) and our framework reflects this by including intention to vaccinate as a factor associated with series initiation (Radisic et al., 2016.

Based on review findings and guided by the Health Belief Model, (Skinner et al., 2015) we also included parental perceived benefits of the HPV vaccine and parental beliefs about their child's susceptibility to HPV and HPV-related diseases in the framework (Galbraith et al., 2016; Holman et al., 2014; Loke et al., 2017; Ryan et al., 2018; Trim et al., 2012; Valentino and Poronsky, 2016). We included perceived need since beliefs that a child is too young for the vaccine (Bartlett and Peterson, 2011; Holman et al., 2014; Trim et al., 2012) or the vaccine is not needed if the child is not sexually active (Bartlett and Peterson, 2011; Trim et al., 2012) were barriers to initiation in reviews. Finally, guided by SCT, we synthesized parental beliefs about effectiveness and safety (Bartlett and Peterson, 2011; Galbraith et al., 2016; Kessels et al., 2012; Kim and LeClaire, 2017; Loke et al., 2017; Small et al., 2014; Trim et al., 2012; Valentino and Poronsky, 2016; Vollrath et al., 2018) as outcomes expectations, or judgements about the likely outcome of vaccination (Montano and Kasprzyk, 2015). Our framework shows parents must expect that vaccination will be safe and effective in protecting against HPV and HPV-related diseases when initiating the series.

Adolescent interaction with the healthcare system and adolescent receipt of other adolescent vaccines were significantly associated with vaccine initiation (Bartlett and Peterson, 2011; Kessels et al., 2012; Radisic et al., 2016; Small et al., 2014; Trim et al., 2012; Vollrath et al., 2018). These factors are included as adolescent behaviors in the framework and as parent behaviors since adolescents often require caretakers to take them to appointments and consent to vaccinations. We chose not include additional parent behaviors that were associated with vaccination outcomes (familial decision-making, discussing the vaccine with son). Instead, we listed only those health-enhancing behaviors (Kelder et al., 2015) that involve the healthcare system.

Our framework includes only provider recommendation of the HPV vaccine at the provider level. In reviews, a provider's recommendation was associated with both initiation and completion (Bartlett and Peterson, 2011; Galbraith et al., 2016; Gallagher et al., 2016; Holman

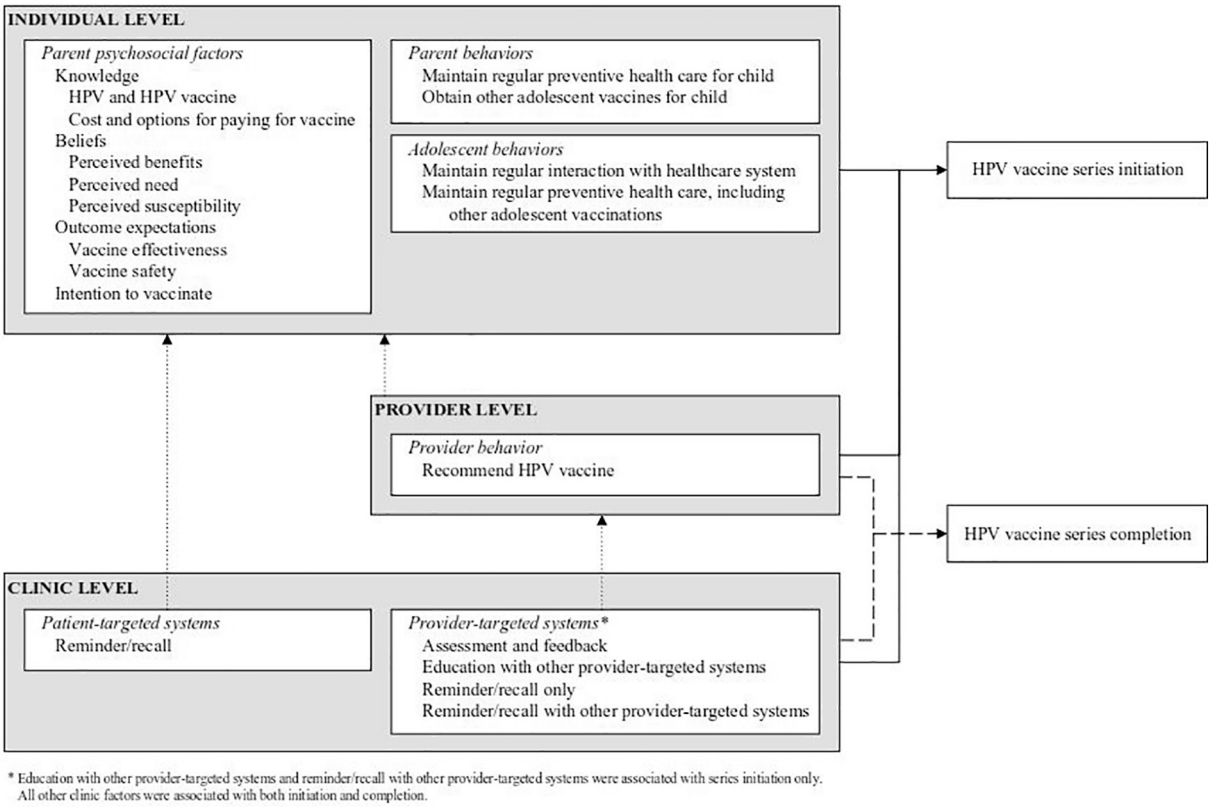


Fig. 2. Multilevel model of factors associated with HPV vaccination among adolescents ages 9–17 years in the U.S.

et al., 2014; Kessels et al., 2012; Kim and LeClaire, 2017; Loke et al., 2017; Ryan et al., 2018; Small et al., 2014; Valentino and Poronsky, 2016; Vollrath et al., 2018). In the framework, we link recommendations to the individual level as they can act as a cue to action (Skinner et al., 2015) influencing parental decisions to vaccinate. Finally, we include both patient-targeted systems and provider-targeted systems in the framework noting their associations with initiation and completion, (Niccolai and Hansen, 2015; Rosen et al., 2018; Ryan et al., 2018; Vollrath et al., 2018; Walling et al., 2016) and we show the influences patient reminder/recall systems can have on parents and the influences provider-targeted systems can have on provider behaviors.

4.2. Intervention development

Identifying factors associated with HPV vaccine initiation and completion and understanding the relations between levels is key to developing multilevel interventions that can increase HPV vaccination coverage and reduce HPV-related diseases. Our framework illustrates how factors relate to the outcomes and how factors can interact to create change. For example, parent reminders may act as motivational cues to action by including short messages addressing important psychosocial factors as opposed to stating only the date and time for an upcoming appointment. Strategically worded text messages have been shown to increase recipients' perceived susceptibility to viruses and to increase parental intention to vaccinate against HPV (McGlone et al., 2013; McGlone et al., 2017).

Because the framework combines salient factors associated with HPV vaccination from reviews focused on diverse populations, it provides a starting point for researchers and program planners interested in developing programs to increase vaccination in their communities. The framework can help researchers and planners avoid the “black box” in intervention development where mechanisms of change are unclear. Instead, planners can identify salient psychosocial factors, for example, and select appropriate behavior change techniques specific to the factor they aim to address (Bartholomew Eldredge et al., 2016; Kok et al., 2016). However, some factors specific to subpopulations may not be included in this framework. Researchers and planners must still engage with their communities and stakeholders to ensure their programs are appropriate (Bartholomew Eldredge et al., 2016). Specifically, engaging in community-based participatory research (CBPR) can ensure community members and stakeholders are involved in all stages of intervention development, implementation, evaluation, and dissemination (Viswanathan et al., 2004). Researchers and program planners have successfully employed CBPR and partnered with communities to assess needs, develop interventions, and implement cancer prevention programs, including HPV vaccination interventions, in diverse settings (Baezconde-Garbanati et al., 2017; Braun et al., 2015; Hou and Cao, 2018; Lai et al., 2017).

4.3. Future research

Our systematic review revealed gaps in the literature at the individual-, provider-, and clinic-levels. We describe future research needed to 1) link the significant body of literature on parental intentions to vaccination behavioral outcomes, 2) identify provider psychosocial factors associated with recommendation behaviors and subsequent uptake, 3) understand factors that influence implementation and adoption of system-level evidence-based interventions within clinics, 4) study factors associated with vaccine series completion, and 5) identify adolescent psychosocial and behavioral factors associated with vaccination outcomes.

First, primary studies in diverse populations have described correlates and predictors of parental intentions to vaccinate their adolescent children (Askelson et al., 2010; Baldwin et al., 2013; Dempsey et al., 2011; Kang and Moneyham, 2011; Lechuga et al., 2011; Lechuga et al., 2014). However, only one review went beyond describing correlates of parental intentions and described the association between parental intentions and HPV vaccination outcomes (Radisic et al., 2016). This lack

of attention to the relation between parental intentions and HPV vaccination outcomes is surprising. This gap represents a lost opportunity to link previous findings about intentions to behavioral outcomes. Based on theory, this is an important gap since intentions may act as a mediator between psychosocial variables, such as attitudes and beliefs, and HPV vaccination (Montano and Kasprzyk, 2015). A clear understanding of the associations between intentions, other psychosocial factors, and vaccination outcomes can help refine the current framework of vaccination and inform future interventions.

Provider recommendation is a well-documented predictor of HPV vaccination (Bartlett and Peterson, 2011; Galbraith et al., 2016; Gallagher et al., 2016; Holman et al., 2014; Kessels et al., 2012; Kim and LeClaire, 2017; Loke et al., 2017; Ryan et al., 2018; Small et al., 2014; Valentino and Poronsky, 2016; Vollrath et al., 2018). However, a shift in focus is needed moving away from focusing strictly on provider recommendation behaviors to examining why providers differentially recommend the vaccine for patients based on age, sex, or other factors and why they communicate differentially with parents (Shay et al., 2018). Studies examining the psychosocial factors associated with provider recommendations would provide a deeper understanding of the context of the patient-provider interaction (Gilkey and McRee, 2016; Gilkey et al., 2016; Shay et al., 2016). Identifying psychosocial correlates of provider behaviors was beyond the scope of this review. However, the few reviews that described findings from studies of predictors of provider recommendation found that provider knowledge, beliefs, personal discomfort discussing sexual health with parents, and concern about cost were associated with recommendation behaviors (Holman et al., 2014; Valentino and Poronsky, 2016). Exploring these factors in more depth can inform provider-level interventions that can enhance vaccine recommendation quality and provider communication with parents.

Our review highlights important clinic-level systems associated with increased HPV vaccination coverage. These include provider assessment and feedback systems and patient reminder systems, (Walling et al., 2016) both recommended by The Guide to Community Preventive Services (The Community Guide) to increase vaccination behaviors (Community Preventine Services Task Force, n.d.). Successful implementation of *The Community Guide* recommended strategies and of cancer control and prevention strategies, such as HPV vaccination interventions, often depend on clinic-level factors such as leadership engagement and organizational culture (Liang et al., 2015; Price et al., 2010). Alternatively, clinic-level characteristics that can hinder implementation of these strategies include competing demands within the clinic, limited resources, limited organizational support, or other practices that work against or fail to incorporate the new systems (Glasgow et al., 2004; Winterbauer et al., 2015). Thus, future research is needed to understand factors that influence the adoption and implementation of these clinic-level systems to increase HPV vaccination. Implementation science and implementation frameworks can help interventions developers or clinic stakeholders identify clinic-level factors relevant to adoption and implementation outcomes and develop implementation strategies to increase adoption and implementation of these systems (National Institutes of Health, n.d.).

The lack of parent-level psychosocial factors and provider-level factors, other than recommendation, associated with completion in the reviews highlights the need for studies focused on these factors to inform multilevel intervention development. While clinic-level systems such as patient reminders are promising interventions to increase completion (Chao et al., 2015; Walling et al., 2016) a more robust understanding of the multilevel factors associated with completion is critical. This is important given ACIP recommendations moving from a three dose series to a two dose series for those under 15 years old (Centers for Disease Control and Prevention, n.d.).

Finally, future research focusing on adolescent-level psychosocial factors and behaviors associated with HPV vaccination outcomes will be particularly important as policy-makers debate whether to eliminate parental consent for adolescent vaccinations (Haddad et al., 2018; Silverman et al., 2019). The Society for Adolescent Health and Medicine supports adolescent consent for vaccination, (English et al., 2013) yet research is lacking on the effectiveness of adolescent consent in increasing vaccination rates (Fisher et al., 2019). Identifying adolescent psychosocial and behavioral factors associated with HPV vaccine initiation and completion can significantly impact this research landscape.

4.4. Limitations

This review did not capture research not yet incorporated into reviews or reviews published since the search date. Additional themes or factors may emerge from continued research. While factors associated with vaccination may become more or less important over time, we chose not to weigh factors found in more recent reviews over factors identified in older reviews. Similarly, our findings do not include conclusions on the strength of the associations within reviews or across reviews. For example, Tables 2 and 3 depict factors associated with vaccination outcomes, but while consistency of assessment may signal the robustness of the association, frequency of assessment does not imply degree of the associations (effect size). Further, some clinic-level best practices for increasing vaccination, such as others described by *The Community Guide*, (Community Preventine Services Task Force, n.d.) were not included in this systematic review. Because our focus was not specifically on interventions, this review did not capture some Community Guide best practices. Limiting the search to HPV vaccination alone may have affected our ability to identify best practices related to improving adolescent vaccination outcomes in general.

In our review, we listed all factors associated with vaccination outcomes supported by ≥ 2 primary studies from integrative, systematic, and literature reviews that included different populations, study designs, and research questions. This approach has some limitations. First, nuanced differences between subpopulations may be lost in data synthesis. Second, differing research questions, populations, settings, and methodologies may mean that reviews did not cover the entire literature body that assessed HPV vaccination outcomes among adolescents in the U.S. leaving out some factors from our synthesis. Finally, we chose not to weigh findings from some reviews over others based on review type or AMSTAR response options for systematic reviews. This approach has limitations if the methodological rigor of reviews significantly differed. However, as previously noted, no tool exists to compare rigor across review types since each type has different methods and objectives. Among systematic reviews, AMSTAR assessments revealed that only five included gray literature searches. This points to the potential for publication bias in the other reviews. AMSTAR responses were based solely on author reporting and may not reflect the methods actually used for a review if authors' statements were less explicit than required to confirm AMSTAR elements.

5. Conclusion

In summary, an updated synthesis of the multilevel factors associated with HPV vaccine initiation and completion among U.S. adolescents is needed. Our systematic review and multilevel framework depict salient factors including parent knowledge, beliefs, outcome expectations, and intentions; parent behaviors; provider recommendation; and patient- and provider-targeted systems that can be modified and targeted through interventions to increase HPV vaccination coverage and reach Healthy People 2020 goals. Future research is needed to empirically link parental intentions to vaccinate and vaccination outcomes, to assess correlates of provider recommendation behaviors and subsequent vaccine uptake among patients, and to identify clinic factors associated with successful implementation of clinic-level systems shown to improve HPV vaccination.

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Appendix A. Supplementary data

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