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Parents' uptake of human papillomavirus vaccines for their children: a systematic review and meta-analysis of observational studies

Peter A Newman,[1] Carmen H Logie,[1] Ashley Lacombe-Duncan,[1] Philip Baiden,[2] Suchon Tepjan,[1] Clara Rubincam,[1] Nick Doukas,[1] Farid Asey[1]

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CHL, AL-D and PB contributed equally.

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[1]Centre for Applied Social Research, Factor-Inwentash Faculty of Social Work, University of Toronto, Toronto, Ontario, Canada
[2]School of Social Work, The University of Texas at Arlington, Arlington, Texas, USA

Correspondence to
Dr. Peter A Newman;
p.newman@utoronto.ca

ABSTRACT

Objective To examine factors associated with parents' uptake of human papillomavirus (HPV) vaccines for their children.

Design Systematic review and meta-analysis.

Data sources Cochrane Library, AIDSLINE, CINAHL, EMBASE, PsycINFO, Social Sciences Abstracts, Ovid MEDLINE, Scholars Portal, Social Sciences Citation Index and Dissertation Abstracts International from inception through November 2017.

Methods We included studies that sampled parents and assessed uptake of HPV vaccines for their children (≤18 years) and/or sociodemographics, knowledge, attitudes or other factors associated with uptake. Study risk of bias was assessed using the Effective Public Health Practice Project tool. We pooled data using random-effects meta-analysis and conducted moderation analyses to examine variance in uptake by sex of child and parent.

Results Seventy-nine studies on 840 838 parents across 15 countries were included. The pooled proportion of parents' uptake of HPV vaccines for their children was 41.5% (range: 0.7%–92.8%), twofold higher for girls (46.5%) than for boys (20.3%). In the meta-analysis of 62 studies, physician recommendation (r=0.46 (95% CI 0.34 to 0.56)) had the greatest influence on parents' uptake, followed by HPV vaccine safety concerns (r=−0.31 (95% CI −0.41 to −0.16)), routine child preventive check-up, past 12 months (r=0.22 (95% CI 0.11 to 0.33)) and parents' belief in vaccines (r=0.19 (95% CI 0.08 to 0.29)). Health insurance-covered HPV vaccination (r=0.16 (95% CI 0.04 to 0.29)) and lower out-of-pocket cost (r=−0.15 (95% CI −0.22 to −0.07)) had significant effects on uptake. We found significant moderator effects for sex of child.

Conclusions Findings indicate suboptimal levels of HPV vaccine uptake, twofold lower among boys, that may be improved by increasing physician recommendations, addressing parental safety concerns and promoting parents' positive beliefs about vaccines, in addition to expanding insurance coverage and reducing out-of-pocket costs. Limitations of this meta-analysis include the lack of intervention studies and high risk of bias in most studies reviewed. Further studies should disaggregate HPV vaccine uptake by sex of child and parent.

Strengths and limitations of this study

- ► This is the first systematic review and meta-analysis to focus on parents' uptake of human papillomavirus (HPV) vaccines for their children, more than 10 years after initial licensure of an HPV vaccine.
- ► Our findings provide pooled estimates of HPV vaccine uptake across 79 studies (n=840 838) conducted in 15 countries, indicating modest (41.5%) overall uptake with twofold higher uptake for girls than for boys.
- ► The majority of studies had a high or moderate risk of bias; however, moderation analysis by risk of bias revealed no significant differences in HPV vaccine uptake.
- ► Some meta-analyses of correlates of parents' uptake of HPV vaccines for their children were based on relatively few studies, but we used random-effects models to compensate for clinical and methodological diversity among studies, and the majority of correlates were based on six or more primary studies.
- ► The risk of publication bias cannot be excluded as 79 studies met the inclusion criteria, but 62 provided sufficient data for meta-analysis; however, there was no significant difference in uptake between studies included and excluded.

INTRODUCTION

Human papillomavirus (HPV) is the most prevalent sexually transmitted infection in the world. HPV infection accounts for the majority of cervical and vaginal cancers among women, and of oropharyngeal and anal cancers among men and women.[1] HPV infection also accounts for nearly half of vulvar cancer among women and penile cancer among men.[1] The bivalent (2vHPV) and quadrivalent HPV vaccine (4vHPV) were licensed in the USA in 2006 for girls and 4vHPV was licensed in 2009 for boys. The nine-valent HPV vaccine (9vHPV) was licensed for girls and boys in 2014. 4vHPV or

9vHPV is recommended for girls and boys age 11 years or older, and women and men through age 26 who have not previously been vaccinated, to prevent HPV infection.[2]

Increasing evidence supports the safety and effectiveness of HPV vaccination in reducing vaccine-type HPV infections at the population level. A meta-analysis across nine high-income countries that recommend HPV vaccination of girls indicated that in those countries with female HPV vaccination coverage of 50% or greater, vaccine-type infections decreased by 68%, with evidence suggesting cross-protection and herd effects.[3] However, in countries with female HPV vaccine coverage lower than 50%, vaccine-type infections decreased by 50%, with no evidence of cross-protection or herd effects.[3] According to the WHO, the HPV vaccine was on the national schedule or reimbursed in 74 countries by 2016,[4 5] although coverage among girls and young women varied greatly by region—from 1.1%–1.2% in Africa and Asia, to 31.1% in Europe, to 35.6% in North America for series completion.[6] While it is estimated that 9vHPV,[7] along with newer HPV vaccination schedules requiring two doses,[8 9] will improve health outcomes and cost-effectiveness of HPV vaccination for both men and women, accelerating uptake remains crucial to realising the public health benefits of HPV vaccination.

As the prevalence of HPV infection is highest among young people, HPV vaccination is recommended for preadolescent boys and girls, ideally prior to sexual debut.[10] Accordingly, parents play a pivotal role in uptake of HPV vaccines.[11] The target age group presents particular challenges for HPV vaccine uptake, including more scrutiny of HPV vaccines than traditional infant vaccines.[8] Thus in addition to structural and health system issues (eg, cost, insurance coverage, delivery strategies) that contribute to low coverage of HPV vaccines globally,[5] the broader context of vaccine hesitancy suggests that parents' knowledge, attitudes and beliefs about HPV and vaccines may have a substantial influence on uptake.[8] Nevertheless, limited evidence documents factors associated with parents' uptake of HPV vaccines for their children, particularly outside North America.

Earlier research both predating and following initial introduction of HPV vaccines identified factors associated with parents' HPV vaccine acceptability and intentions to have their children vaccinated.[12 13] The decade elapsed since the first HPV vaccine was licensed, and the documented real-world challenges in the introduction and uptake of HPV vaccines globally indicate the importance of synthesising evidence on factors associated with HPV vaccine uptake.[5] We build on previous descriptive reviews of HPV vaccine uptake by conducting a meta-analysis to estimate parents' uptake of HPV vaccines for their children and factors that influence parents' uptake. In light of emerging public health recommendations for routine HPV vaccination of boys as well as girls,[2] and the substantially lower coverage in boys,[14] we included boys in all analyses and assessed sex differences in uptake by child and parent.

Objectives

The purpose of this meta-analysis was to synthesise results from quantitative correlational investigations of parents' uptake of HPV vaccines for their children. Specifically, we aimed to (1) quantify the levels of parents' HPV vaccine uptake for their children; (2) examine factors correlated with parents' uptake of HPV vaccines for their children; and (3) identify possible moderating influences of sex of child and parent on uptake.

METHODS

We conducted a systematic search of the scientific literature and performed random-effects meta-analysis to examine factors associated with parents' uptake of HPV vaccines for their children. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[15] and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[16]

Selection criteria

We specified eligibility criteria for the search and meta-analyses using the population, intervention (or exposure), comparison, outcome and study design (PICOS) framework. We defined the following key question to be explored: What are the factors associated with parents' uptake of ≥1 dose of HPV vaccines for their children? We specified the population of interest as parents or guardians of children aged ≤18 years. The intervention or exposure was ≥1 dose of HPV vaccine uptake for children, with the comparator as no doses of HPV vaccine uptake.

The primary outcome of analysis was parents' uptake of ≥1 dose of HPV vaccine for their children. The secondary outcomes were factors associated with parents' HPV vaccine uptake for their children, including parents' sociodemographic characteristics, HPV risk history (eg, genital warts), HPV vaccine and HPV-related disease knowledge and awareness (eg, HPV vaccine awareness), vaccine attitudes and beliefs (eg, safety concerns, perceived benefits), child preventive healthcare utilisation (eg, routine check-up), healthcare provider factors (eg, healthcare provider recommendation), and structural factors (eg, health insurance coverage of HPV vaccination).

We included randomised controlled trials (RCTs), cluster RCTs, non-RCTs, longitudinal studies, cohort studies and cross-sectional studies that explored parents' uptake of HPV vaccines for their children. There were no language, geographical or time restrictions. Studies were excluded that did not report original data (eg, reviews, editorials) or examine parents' uptake of HPV vaccines for their children (eg, acceptability or intention to vaccinate).

Search strategy

We conducted a comprehensive search across multiple electronic databases from inception to locate studies meeting the inclusion criteria: Cochrane Library, Cochrane Central Register of Controlled Trials, AIDSLINE, CINAHL, EMBASE, PsycINFO, Social Sciences Abstracts, Ovid MEDLINE, Scholars Portal, Social Sciences Citation Index, Dissertation Abstracts International, Applied Social Sciences Index and Abstracts, CSA Sociological Abstracts, ProQuest Research Library, CSA Social Services Abstracts, and AgeLine. The last search date was November 2017. Search terms were developed in consultation with a research librarian and chosen to draw on the broadest pool of potential studies. A sample of the search string and keywords used is listed in online supplementary file 1. We also searched for additional relevant studies by reviewing references from the included articles (ie, 'snowballing').

Data extraction

Two authors (ND and AL-D, or AL-D and PB) independently screened all titles and abstracts for inclusion. When the first reviewer determined the study might meet the inclusion criteria based on the study objectives, the full text was obtained. Two reviewers (ND and AL-D, or AL-D and PB) then independently assessed each study for inclusion based on study type and outcome measures, documenting reasons for exclusion. A consensus approach with input from the senior investigator (PAN) was used to resolve disagreements.

We developed a data extraction form using Microsoft Excel. Two of the five reviewers (ND, AL-D, PB, ST and FA) independently extracted the following data: study information (ie, year of publication, author and journal); descriptive data (ie, sample size, country and participant demographics); study aims, design and methods; outcomes/key findings; and study funding sources and reported conflicts of interest (COIs). Reviewers explored data regarding any variables examined as possible correlates of parents' HPV vaccine uptake for their children. All members of the research team then developed a list of themes related to HPV vaccine uptake based on a review of the included studies.

Risk of bias

Reviewers independently assessed the risk of bias in individual studies using the Effective Public Health Practice Project (EPHPP) 'Quality Assessment Tool for Quantitative Studies'.[17] The EPHPP tool has been applied in numerous systematic reviews and has demonstrated inter-rater reliability for both individual domains and overall score.[17] We modified the EPHPP for use with cross-sectional studies and examined selection bias (representativeness of sample, participation rate), data collection method (validity, reliability) and study design.[18] Reviewers followed the EPHPP rubric to assess whether each component had low, moderate or high risk of bias, with any disagreements resolved by consensus with the senior investigator (PAN).[17] For the purpose of moderation analysis, studies with low and moderate risk of bias were grouped together and compared with studies with high risk of bias. No studies were excluded on the basis of risk of bias.

We assessed each study as to whether commercial entities were declared as providing support for the work reported in the study. Additionally, we indicated potential COIs on the part of study authors, including associations with commercial entities that could be viewed as having an interest in the general area of vaccines (in the 3 years before manuscript submission), per International Committee of Medical Journal Editors guidelines.[19]

Data synthesis and analysis

We calculated the pooled proportion of HPV vaccine uptake using the proportion of HPV vaccine uptake reported in each included study. We then conducted meta-analysis to critically evaluate and quantitatively synthesise evidence across studies that examined similar correlates of parents' HPV vaccine uptake for their children. Combining the results of multiple studies increases statistical power to improve estimates of effects in a larger population. We used the Comprehensive Meta-Analysis Software V.2 (Englewood, New Jersey, 2004) to calculate effect sizes for each variable, with a random-effects model to compensate for clinical and methodological diversity among studies. Random-effects models are more conservative than fixed-effect models. Rather than presuming one true effect size, in random-effects models it is assumed that the heterogeneity of studies will contribute to differences in effects between studies, and that there is a distribution of true effect sizes across similar but not identical studies.[20] Random-effects models account for the fact that the studies included were conducted by different investigators in different locations at different times, rather than by the same investigator with the same population at a given time point. To derive a global estimate of the correlation of each variable with HPV vaccine uptake, we combined coefficients across studies, and present a summary effect that estimates that distribution's mean. We calculated the Q statistic to assess homogeneity of correlations across studies and the I^2 index to assess the degree of heterogeneity between studies using Higgins and Thompson's guidelines,[21] which indicate that I^2 values of 25% represent low, 50% medium and 75% high heterogeneity.

Given disparities in HPV vaccine uptake for boys and girls, we assessed both sex of child and sex of parent as moderator variables in meta-analysis. Moderation analysis allows for evaluating the impact of a covariate on the outcome variable while holding other covariates constant, and helps to explain heterogeneity in effect sizes in meta-analysis.[20] The Comprehensive Meta-Analysis V.2 software enables testing of categorical variables as moderators in order to compare effect sizes between two groups.

All studies that provided sufficient data regarding correlates of parents' HPV vaccine uptake for their children were included in the meta-analysis. For studies that did not report sufficient information to enable inclusion in meta-analysis, we contacted study investigators to provide missing and unreported data. We did not conduct meta-analysis on dichotomous (intervention vs control group) data as the vast majority of studies did not evaluate interventions to increase HPV vaccine uptake. However, if an intervention was implemented as part of the study design and baseline/preintervention uptake data were provided, this uptake percentage was used in calculating the pooled proportion of parents' HPV vaccine uptake for their children.

Patient and public involvement

No patients were involved in the development of the research question, development of outcome measures, design or conduct of this study. No patients were asked to advise on interpretation or writing up of results. There are no plans to involve patients in the dissemination of the results of this study.

RESULTS

Study selection

The literature search yielded 1345 studies with 100% agreement among reviewers (ND, AL-D and PB) in selecting 271 relevant studies, 79 of which met the inclusion criteria. Of the relevant studies, 192 full-text articles were excluded based on the following reasons: 96 assessed intention to vaccinate rather than uptake, 69 did not focus on parents' HPV vaccine uptake for children, 12 were not quantitative studies, 6 were reviews, 5 contained insufficient data and 4 studies were duplicates (figure 1).

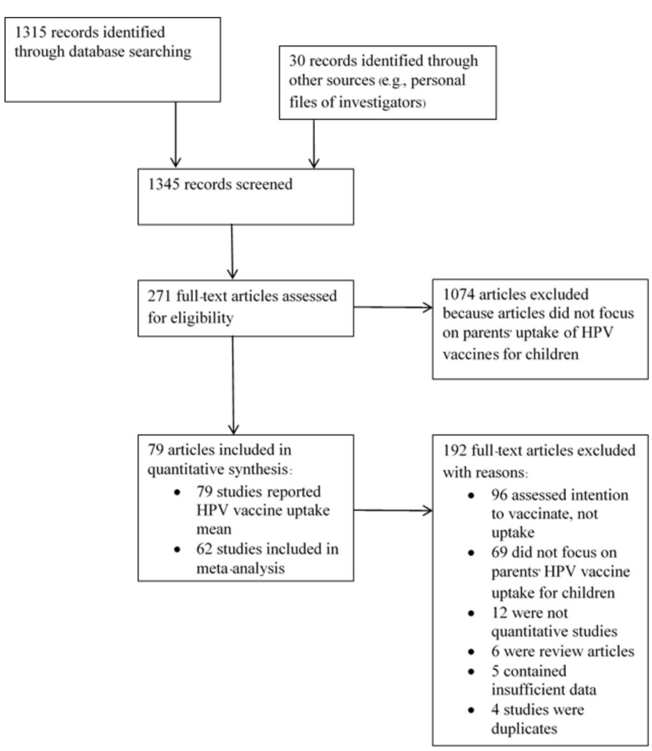

Figure 1 PRISMA flow chart of the searched, identified and included studies of parents' uptake of human papillomavirus (HPV) vaccination for their children. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Study characteristics

The 79 included studies[22–100] were all published in English. The majority (69.6%; n=55) were conducted in the USA,[23 27 34 38–41 45 46 48–54 56–62 64 65 67–69 71–77 80–94 97–99] with four conducted in Canada (5.1%),[24 28 36 37] four in the Netherlands (5.1%),[26 33 35 55] two in Denmark,[22 29] two in Norway,[30 31] two in Puerto Rico,[63 70] and one each in Austria,[43] Fiji,[44] Hong Kong,[96] Italy,[47] Kenya,[66] South Africa,[42] Tanzania,[32] Turkey,[100] United Arab Emirates[95] and Vietnam.[25]

The majority (57.0%; n=45) of studies assessed parents' uptake of HPV vaccines for girls only,[22–26 29–39 42 44 45 48 52 56–58 61 65–68 71–73 76 77 80 81 83 85 86 88 92–96] 30.4% (n=24) for both boys and girls,[27 28 40 41 43 46 49–51 53 54 56 59 62 64 75 78 79 82 87 89–91 100] and 12.7% (n=10) for boys only.[47 60 63 69 70 74 84 97–99]

In terms of the sex of the parents/caregivers surveyed, 55.7% (n=44) of studies included mothers and fathers,[23 26 30–32 35–37 40–44 46 47 51–54 57 59 61 63–65 67 69 70 72 74 76 78 81 83–85 88 91 93 94 96–98] 30.4% (n=24) only mothers,[22 25 29 33 39 45 49 50 55 58 62 66 68 71 73 77 79 80 87 89 90 95 99 100] and 13.9% (n=11) did not specify parent's/caregiver's sex.[24 27 28 34 38 48 56 60 82 86 92] The majority of studies (92.4%; n=73) used HPV vaccine initiation (≥1 dose) as the primary outcome,[22–24 26–43 45–54 56 57 59–82 84 85 87–100] while 7.6% (n=6) specified only three-dose series completion.[25 44 55 58 83 86] Individual study aims and recruitment methods are reported in online supplementary file 2.

Pooled proportion of HPV vaccine uptake

All studies (n=79) quantified parents' (n=840 838) uptake of HPV vaccines for their children. Table 1 lists the study characteristics and mean uptake of HPV vaccines. Most studies were cross-sectional in design, with seven longitudinal studies,[26 33 40 48 52 72 98] one retrospective cohort study,[29] one case–control study,[32] one quasi-experimental (single-group, pre-post design) study,[39] one clustered, non-randomised controlled pragmatic trial[62] and one cluster randomised trial.[45] Sample sizes ranged from 43[45] to 254 489[99] (median (M)=617.0), with 88.6% (n=70) ranging from 43[45] to 8652[50] (M=519.5) and 11.4% (n=9) ranging from 15 049[34] to 254 489[99] (M=65 926).

The pooled proportion of parents' uptake of HPV vaccines for their children ranged from 0.7%[100] to 92.8%[22] across studies, with overall mean uptake of 41.5% (SD=24.2). The pooled proportion of uptake of HPV vaccines for girls (46.5%) was significantly greater than uptake for girls and boys combined (39.8%) and uptake for boys (20.3%; $F(2, 76)=4.92$, P=0.010). The average uptake of HPV vaccines among six low-income and middle-income countries[25 32 42 44 66 100] was 51.6% compared with 40.6% in 73 high-income countries[22–24 26–31 33–41 43 45–65 67–99]; however, this difference failed to achieve statistical significance ($F(1, 77)=1.13$, P=0.292). Comparison of uptake of HPV vaccines between studies with sample sizes ranging from 43 to 9554 ($\bar{x}$=39.8%)

Table 1 Studies assessing parents' uptake of HPV vaccines for their children, study characteristics, risk of bias and sponsorship, ordered by mean vaccine uptake (n=79)

HPV vaccine uptake, x̄* (%)	Number of doses	Source of uptake report	Author(s), year	Sex of parent (female/male) (%)	Parent's age, years x̄±SD (range)	Sex of child vaccinated	HPV vaccine uptake by sex of child	Child age, years x̄ (range)	Sample size of parents†	Country	Included in meta-analysis	Risk of bias	Commercial sponsor-ship of study	COI‡
92.8	≥1	Admin	Slåttelid Schreiber *et al*, 2015[22]	F: 100	NS	F	–	12	65 926†	Denmark	Y	High	N	Y
89.0	≥1	Parent	Perkins *et al*, 2010[23]	F: 95 M: 5	43.2 (31–62)	F	–	15.0 (11–18)	76	USA	N	Low/Moderate	Y	N
88.2	1	Parent	Krawczyk *et al*, 2015[24]	NS	40.2±6.0 (26–58)	F	–	9–10	774	Canada	Y	High	N	Y
86.8	3	Parent	Paul *et al*, 2014[25]	F: 100	NS	F	–	11	536	Vietnam	Y	High	N	N
82.0	≥1	Parent	Alberts *et al*, 2017[26]	F: 88 M: 12	*M*=45	F	–	13	1309	The Netherlands	Y	Low	N	Y
82.0	≥1	Parent	Brown *et al*, 2017[27]	NS	NS	F, M	F: 71.4 M: 88.6	*M*=12 (10–17)	200	USA	N	High	N	N
81.9	≥1	Admin	McClure *et al*, 2015[28]	NS	N/S	F, M	F: 84.9 M: 79.0	11–12	1440†	Canada	Y	High	N	N
80.0	1	Admin	Widgren *et al*, 2011[29]	F: 100	NS	F	–	NS	33 838†	Denmark	Y	Low/Moderate	NS	NS
78.3	≥1	Admin	Feiring *et al*, 2015[30]	F: NS M: NS	NS	F	–	12	84 319†	Norway	Y	High	N	N
78.2	1	Admin	Hansen *et al*, 2015[31]	F: NS M: NS	NS	F	–	12–13	90 842†	Norway	Y	High	N	Y
74.3§	≥1	Parent	Watson-Jones *et al*, 2012[32]	F: 78.0 M: 22.0	38.2	F	–	*M*=13 (IQR 13–15)	404	Tanzania	Y	Low/Moderate	N	Y
73.0	≥1	Admin	Pot *et al*, 2017[33]	F: 100	44±4.3	F	–	12–18	8026	The Netherlands	Y	High	NS	N
66.7	≥1	Parent	Hofstetter *et al*, 2014[34]	NS	NS	F	–	15.6 (11–19)	15 049	USA	Y	High	Y	Y
66.0	≥1	Parent	Gefenaite *et al*, 2012[35]	F: NS M: NS	44 (35–55)	F	–	13–16	469	The Netherlands	Y	High	N	N
65.1	≥1	Parent	Ogilvie *et al*, 2010[36]	F: 84.9 M: 14.9	Mo: 40–49	F	–	11	2025	Canada	Y	Low/Moderate	N	Y
65.0	≥1	Parent	Buchan *et al*, 2011[37]	F: 84.6 M: 15.4	NS	F	–	13	208	Canada	N	High	NS	NS
64.0	≥1	Parent	Staras *et al*, 2014[38]	NS	NS	F	–	9–19	2422	USA	Y	High	N	N
61.0	≥1	Parent	Morales-Campos and Parra-Medina, 2017[39]	F: 100	38±7.8	F	–	11–17	317	USA	Y	High	N	N
60.0	≥1	Parent	VanWormer *et al*, 2017[40]	F: 83 M: 17	43.7±6.1	F, M	F: 62 M: 58	11–17	221	USA	Y	High	N	N
59.0¶	≥1	Parent	Rand *et al*, 2011[41]	F: 81.0 M: 19.0	≤40: 37% >41: 63%	F, M	NS	11–17	430	USA	Y	High	N	Y
58.6	≥1	Admin	Botha *et al*, 2014[42]	F: NS M: NS	NS	F	–	9–12	3465	South Africa	N	High	Y**	N
58.6	1	Parent	Borena *et al*, 2016[43]	F: 90 M: 9.6	40.8±5.7	F, M	F: 59.0 M: 51.8	9	449	Austria	Y	High	NS	N
58.0	3	Parent	La Vincente *et al*, 2015[44]	F: 80.2 M: 13.3 NS: 4.8	*M*=40 (IQR 36–43)	F	–	9–12	293	Fiji	N	High	N	Y
56.0	≥1	Parent	Winer *et al*, 2016[45]	F: 100	41±10	F	–	9–12	43	USA	N	Low	N	N

Continued

Table 1 Continued

HPV vaccine uptake, x̄* (%)	Number of doses	Source of uptake report	Author(s), year	Sex of parent (female/ male) (%)	Parent's age, years x̄±SD (range)	Sex of child vaccinated	HPV vaccine uptake by sex of child	Child age, years x̄ (range)	Sample size of parents†	Country	Included in meta-analysis	Risk of bias	Commercial sponsor-ship of study	COI‡
54.8	1	Admin	Fu *et al*, 2017[46]	F: 93.5 M: 6.5	37.9±7.7	F, M	NS	10–12	400	USA	Y	High	N	Y
53.7	≥1	Parent	Bianco *et al*, 2014[47]	F: NS M: NS	42.9 (NS)	M	–	12–18	566	Italy	N	High	NS	N
50.9	≥1	Parent	Cuff *et al*, 2016[48]	NS	NS	F	–	11–12	908	USA	Y	High	N	N
50.0	≥1	Parent	Donahue *et al*, 2015[49]	F: 100	NS	F, M	F: 60.3 M: 39.7	9–13	2185	USA	Y	High	N	Y
49.9	1	Parent	Dorell *et al*, 2010[50]	F: 100	Mo: ≥45	F, M	NS	15 (13–17)	8652	USA	Y	High	N	N
49.0	≥1	Parent	Moss *et al*, 2016[51]	F: 76.8 M: 16.7	Mo: ≥45	F, M	–	13–17	9021	USA	Y	High	N	Y
48.0	≥1	Parent	Nonzee *et al*, 2018[52]	F: 96.3 M: 3.7	Mo: 40–49	F	–	13–17	1779	USA	Y	High	N	N
47.3	≥1	Parent	Gilkey *et al*, 2017[53]	F: 56 M: 44	NS	F, M	NS	11–17	1484	USA	Y	High	Y	Y
47.0	≥1	Parent	Gerend *et al*, 2009[54]	F: 95.0 M: 5	36.0±9.0	F, M	NS	<18	82	USA	Y	High	NS	NS
45.0	3	Parent	van Keulen *et al*, 2013[55]	F: 100	43.4±4.6	F	–	13–14	952	The Netherlands	N	Low/Moderate	N	N
45.0	≥1	Admin	Johnson *et al*, 2017[56]	NS	NS	F, M	F: 57.0 M: 33.0	13–17	18 264†	USA	Y	High	N	N
42.0	1	Parent	Reiter *et al*, 2011[57]	F: 94 M: 6	Mo: 40+	F	–	11–20	647	USA	Y	High	N	Y
41.0	3	Admin	Chao *et al*, 2009[58]	F: 100	42.1±6.4	F	–	9–17	18 275	USA	Y	Low/Moderate	NS	NS
36.3	≥1	Parent	Kepka *et al*, 2015[59]	F: 89.6 M: 10.4	42.9±7.8 (29–67)	F, M	F: 49.1 M: 23.4	11–17	67	USA	Y	High	N	N
34.6	≥1	Parent	Lu *et al*, 2015[60]	NS	NS	M	–	13–17	9554	USA	Y	High	N	N
33.1	≥1	Parent	Reynolds, 2014[61]	F: 94.7 M: 5.3	43.8 (24–65)	F	–	9–18	323	USA	N	High	NS	N
32.9	1	Admin	Sanderson *et al*, 2017[62]	F: 100	Mo: 30–39	F, M	NS	9–18	408†	USA	Y	Low	N	N
31.7	≥1	Parent	Colón-López *et al*, 2015[63]	F: 91.7 M: 8.3	38.6±7.2	M	–	9–17	60	Puerto Rico††	N	High	N	NS
31.7	≥1	Parent	Kepka *et al*, 2015[64]	F: 84.4 M: 15.7	Mo: 40–49	F, M	F: 42.6 M: 20.7	11–17	118	USA	Y	High	N	N
31.3	≥1	Parent	Reiter *et al*, 2010[65]	F: 94 M: 6	Mo: 40–49	F	–	10–17	617	USA	Y	High	N	N
31.1	≥1	Parent	Vermandere *et al*, 2014[66]	F: 100	*M*=35 (IQR 32–40)	F	–	8–18	256	Kenya	Y	High	Y**	N
31.0	≥1	Parent	Cates *et al*, 2010[67]	F: 81.5 M: 18.5	NS	F	–	10–17	696	USA	Y	High	N	NS
31.0	1	Parent	Kadis *et al*, 2011[68]	F: 100	Mo: 40–49	F	–	11–14	496	USA	N	Low/Moderate	N	Y
30.0	≥1	Parent	Perkins *et al*, 2013[69]	F: 80.0 M: 20.0	43.5±8.3	M	–	11–17	120	USA	Y	High	Y	N
29.3	≥1	Parent	Colón-López *et al*, 2016[70]	F: 88.5 M: 11.5	37.7±7.2	M	–	9–17	200	Puerto Rico††	Y	High	N	NS

Continued

Table 1 Continued

HPV vaccine uptake, $\bar{x}$* (%)	Number of doses	Source of uptake report	Author(s), year	Sex of parent (female/male) (%)	Parent's age, years $\bar{x}$±SD (range)	Sex of child vaccinated	HPV vaccine uptake by sex of child	Child age, years $\bar{x}$ (range)	Sample size of parents†	Country	Included in meta-analysis	Risk of bias	Commercial sponsor-ship of study	COI‡
29.0	≥1	Parent	Taylor *et al*, 2014[71]	F: 100	Mo: ≥45	F	–	9–17	86	USA	Y	High	N	NS
28.9	≥1	Admin	Fishman *et al*, 2016[72]	F: 90.5 M: 9.5	41.7±9.2 (23–71)	F	–	13–18	149	USA	Y	High	N	N
28.3	1	Parent	Price, 2013[73]	F: 100	NS	F	–	9–18	106	USA	Y	High	N	NS
28.0	≥1	Parent	Rickert *et al*, 2014[74]	F: 85.9 M: 14.1	41.6	M	–	11–15	249	USA	Y	High	Y	Y
27.7	≥1	Parent	Fuchs *et al*, 2016[75]	F: 100	Mo: 30–39	F, M	NS	9–17	350	USA	N	High	N	N
27.0‡‡	≥1	Parent	Brewer *et al*, 2011[76]	F: 94.3 M: 5.7	Mo: <40	F	–	10–18	567	USA	Y	High	N	Y
26.0	≥1	Parent	Rosenthal *et al*, 2008[77]	F: 100	41 (27–77)	F	–	11–17	153	USA	Y	Low/Moderate	Y	NS
25.8	≥1	Parent	McRee *et al*, 2017[78]	F: 67.8 M: 32.2	Mo: 40–49	F, M	NS	11–17	2156	USA	Y	High	N	Y
25.6	≥1	Parent	Lee *et al*, 2016[79]	F: 100	44.6±7.6	F, M	F: 32.6 M: 18.6	12–17	130	USA	Y	High	N	N
24.0	≥1	Parent	Hertweck *et al*, 2013[80]	F: 100	44	F	–	13–17	68	USA	Y	Low/Moderate	Y	NS
23.1	1	Parent	Guerry *et al*, 2011[81]	F: 89.7 M: 10.3	41.7±7.4 (22–71)	F	–	11–18	503	USA	Y	Low/Moderate	N	Y
22.5	1	Parent	Wong *et al*, 2011[82]	NS	NS	F, M	NS	9–17	2205	USA	Y	High	N	N
22.0	3	Parent	Clark *et al*, 2016[83]	F: 56.7 M: 43.3	Mo: 24–44	F	–	11–17	786	USA	Y	High	N	N
21.4	≥1	Parent	Taylor *et al*, 2014[84]	F: 51.5 M: 48.5	42.2±11.5	M	–	11–17	758	USA	Y	High	Y	Y
19.4	≥1	Parent	Tiro *et al*, 2012[85]	F: 54.6 M: 45.4	Mo: 40–49	F	–	12–17	3615	USA	Y	Low/Moderate	N	N
19.0	3	Parent	Allen *et al*, 2010[86]	NS	NS	F	–	9–17	451	USA	Y	Low/Moderate	N	N
17.0	≥1	Parent	Berenson *et al*, 2017[87]	F: 100	Mo: 30–39	F, M	F: 20 M: 11	9–17	1497	USA	Y	High	N	N
16.5	≥1	Parent	Thompson *et al*, 2012[88]	F: 68.2 M: 30.8	40.0±8.3	F	–	9–17	200	USA	Y	High	N	Y
15.8	≥1	Parent	Gross *et al*, 2015[89]	F: 100	Mo: 30–39	F, M	F: 21.8 M: 9.8	9–17	1372	USA	N	High	N	N
14.9	≥1	Parent	Berenson *et al*, 2014[90]	F: 100	Mo: 30–39	F, M	F: 19.5 M: 10.3	9–17	1256	USA	Y	High	N	N
13.0	≥1	Parent	Horn *et al*, 2010[91]	F: 88.6 M: 11.4	Mo: 30–39	F, M	NS	9–17	325	USA	N	Low/Moderate	NS	NS
13.0	≥1	Parent	Saak, 2011[92]	NS	NS	F	–	12–17	649	USA	Y	High	NS	NS
12.0	≥1	Parent	Reiter *et al*, 2009[93]	F: 93.9 M: 6.1	Mo: ≥40	F	–	10–18	886	USA	Y	Low/Moderate	N	Y
10.3†	≥1	Parent	Gottlieb *et al*, 2009[94]	F: 89.7 M: 10.3	41 (IQR 36–45)	F	–	11–18	886	USA	Y	High	N	Y
9.8	1	Parent	Ortashi *et al*, 2014[95]	F: 100%	32.4±8.2	F	–	NS	640	United Arab Emirates	N	High	NS	NS

Continued

Table 1 Continued

HPV vaccine uptake, $\bar{x}$* (%)	Number of doses	Source of uptake report	Author(s), year	Sex of parent (female/ male) (%)	Parent's age, years $\bar{x}$±SD (range)	Sex of child vaccinated	HPV vaccine uptake by sex of child	Child age, years $\bar{x}$ (range)	Sample size of parents†	Country	Included in meta-analysis	Risk of bias	Commercial sponsor-ship of study	COI‡
9.8	≥1	Parent	Wang *et al*, 2017[96]	F: 74.4 M: 25.6	47.7±5.5	F	–	12–17	988	Hong Kong	Y	Low	N	N
4.2§§	≥1	Admin	Cates *et al*, 2014[97]	F: NS M: NS	NS	M	–	9–13	176 590†	USA	N	High	N	Y
2.0	1	Parent	Reiter *et al*, 2013[98]	F: 52 M: 48	Mo: <45	M	–	11–17	228	USA	Y	Low/Moderate	Y	Y
1.6	≥1	Admin	Hechter *et al*, 2013[99]	F: 100	NS	M	–	9–17	254 489†	USA	Y	High	N	NS
0.7	≥1	Parent	Kose *et al*, 2014[100]	F: 100	32.0±6.5	F, M	NS	0–18	779	Turkey	N	High	NS	NS

*Mean uptake percentage presented for HPV vaccine initiation (≥1 dose), except for six studies that only reported three-dose completion.
†Sample size refers to the number of parents, unless indicated by †, in cases where the data are drawn from administrative databases and refer to the number of children.
‡COI based on the International Committee of Medical Journal Editors guidelines.[19]
§Overall mean calculated on uptake across cases and controls.
¶Overall mean calculated on uptake across children's ages.
**Study vaccine reported as donated by pharmaceutical company.
††An unincorporated territory of the USA, but does not have equal access to all rights and privileges of citizenship. Although officially classified as a high-income country, it has similar health infrastructure deficits and other socioeconomic conditions more typical of some low-income and middle-income countries.
‡‡Longitudinal study, used follow-up mean uptake score.
§§Used preintervention uptake score.
Admin, administrative records; COI, conflict of interest; F, female; HPV, human papillomavirus; M, male; *M*, median; Mo, mode; N, no; NS, not stated; Parent, parent report; $\bar{x}$, mean; Y, yes.

and those ranging from 15 049 to 254 489 ($\bar{x}$=54.2%) revealed a non-significant trend of studies with sample sizes of ≥15 000 reporting higher uptake than studies with sample sizes<15 000 (F(1, 77)=2.89, P=0.095).

Study quality

We assessed risk of bias for all studies: the majority (75.9%; n=60) had a high risk of bias,[22 24 25 27 28 30 31 33–35 37–44 46–54 56 57 59–61 63–67 69–76 78 79 82–84 87–90 92 94 95 97 99 100] 19.0% (n=15) low/moderate risk of bias[23 29 32 36 55 58 68 77 80 81 85 86 91 93 98] and 5.1% (n=4) low risk of bias.[26 45 62 96] No significant difference in parents' uptake of HPV vaccines for their children was identified between studies with low/moderate risk of bias ($\bar{x}$=41.3%) and studies with high risk of bias ($\bar{x}$=41.5%; F(1, 77)=0.002, P=0.967).

Funding and COI

Overall, 11 studies (13.9%) declared funding from commercial entities (all pharmaceutical companies),[23 34 42 53 66 69 74 77 80 84 98] 56 (70.9%) declared funding not including commercial entities,[22 24–28 30–32 35 36 38–41 44–46 48–52 55–57 59 60 62–65 67 68 70–73 75 76 78 79 81–83 85–90 93 94 96 97 99] and 12 (15.2%) did not specify funding.[29 33 37 43 47 54 58 61 91 92 95 100] Twenty-five studies (31.6%)[22 24 26 31 32 34 36 41 44 46 49 51 53 57 68 74 76 78 81 84 88 93 94 97 98] declared or were assessed (ie, if author/coauthor declared a COI in another study included in the review within the stipulated time frame) as having a potential COI, 38 (48.1%) declared no COI,[23 25 27 28 30 33 35 38–40 42 43 45 47 48 50 52 55 56 59–62 64–66 69 72 75 79 82 83 85–87 89 90 96] and 16 (20.3%) did not specify COI.[29 37 54 58 63 67 70 71 73 77 80 91 92 95 99 100] We found no significant difference in uptake of HPV vaccines between studies that declared any funding from commercial entities ($\bar{x}$=38.5%) versus studies that did not declare any commercial funding ($\bar{x}$=42.2%; F(1, 77)=0.19, P=0.668). Similarly, there was no statistically significant difference in HPV vaccine uptake between studies with a potential COI ($\bar{x}$=44.6%) versus those with no COI ($\bar{x}$=44.5%; F(1, 77)=0.62, P=0.435).

Correlates of parents' uptake of HPV vaccines for children

Sixty-two original studies[22 24–26 28–36 38–41 43 45 46 48–54 56–59 62 64–67 69–74 76–88 90 92–94 96 98 99] (n=654 100) measured similar correlates of parents' uptake of HPV vaccines for their children and were included in the meta-analysis (as indicated in table 1). An examination of the pooled proportion of HPV vaccine uptake found no statistically significant difference between studies included in the meta-analysis (n=62; $\bar{x}$=42.0% uptake) and those not included due to insufficient data (n=17; $\bar{x}$=39.6% uptake). Based on the available data, we examined correlations between HPV vaccine uptake and 19 factors, organised thematically in eight domains. Table 2 indicates the weighted mean correlational effect sizes (r) measuring associations with HPV vaccine uptake, 95% CI, the Q test of homogeneity and I^2 index of between-study variability.

Factors positively associated with parents' uptake of HPV vaccines for their children were identified

Table 2 Meta-analysis of correlates of parents' HPV vaccine uptake for their children (n=62 studies; sample size=654 100)

Domain	Factor	Studies (n)	Random-effect size (95% CI)	Homogeneity index, Q	Between-study variability, I^2
Healthcare provider-related	Physician recommendation	21 [40 43*46 49–51 54 56 66 70 73 81 83 84 86 90 93 94 97 98]	0.46 (0.34 to 0.56), P<0.000	690.356, P<0.000	97.103
	Parents' trust in healthcare provider	4 [23 46 86 88]	0.11 (0.01 to 0.21), P=0.026	3.975, P=0.264	24.528
Parental HPV vaccine decision-maker	Mother as HPV vaccine decision-maker (vs both parents)	2 [90*]	0.34 (0.23 to 0.44), P<0.001	0.05, P=0.83	0.000
Parents' vaccine attitudes, beliefs and intentions	Intention to vaccinate child for HPV	4 [23 26 33 96]	0.31 (0.17 to 0.43), P<0.000	41.288, P<0.000	92.734
	HPV vaccine safety concerns	12 [24 38 40 41 46 48 54 64 74 86 93 98]	−0.23 (−0.35 to 0.11), P<0.000	254.017, P<0.000	95.670
	Belief in vaccines in general	14 [24 32 35 36 38 46 49 54 57 65 69 73 74 86]	0.19 (0.08 to 0.29), P=0.001	337.048, P<0.001	96.143
	Perceived HPV vaccine benefits	10 [24 38 46 54 73 74 81 86 93 98]	0.17 (0.10 to 0.24), P<0.000	78.43, P<0.000	88.525
	Anticipatory regret if child not vaccinated	2 [24 98]	0.14 (0.11 to 0.17), P<0.000	0.11 (0.74)	0.000
Preventive healthcare utilisation for child	Routine childhood preventive check-up, past 12 months	8 [49 56 57 60 65 71 82 98]	0.22 (0.11 to 0.33), P<0.001	61.472, P<0.000	88.613
Health insurance/cost	Health insurance coverage of HPV vaccination	10 [52 56 57 63 65 82 88 93 94 98]	0.16 (0.04 to 0.29), P=0.011	49.642, P<0.001	81.870
	Out-of-pocket cost for HPV vaccination	3 [59 82 98]	−0.15 (−0.22 to 0.07), P<0.000	1.013, P=0.603	0.000
Parents' HPV risk history	Parent history of HPV	3 [43*87]	0.16 (0.06 to 0.25), P=0.002	0.737, P=0.692	0.000
	Parent history of receiving a Pap smear	3 [35 58 99]	0.06 (0.004 to 0.107), P=0.036	65.712, P<0.000	95.435
	Parent history of genital warts	3 [58 88 99]	0.05 (0.03 to 0.07), P<0.001	0.79, P=0.67	0.000
	Parent or family history of abnormal Pap smear	4 [58 87 88 99]	0.02 (0.01 to 0.04), P=0.012	4.191, P=0.242	28.425
Parents' HPV knowledge and awareness	HPV vaccine knowledge/awareness	9 [25 39 54 72 73 81 82 86 87]	0.14 (0.05 to 0.23), P=0.002	65.889, P<0.000	87.858
	Cervical cancer/HPV knowledge	14 [24 25 35 38 39 43*54 66 69 73 79 87 88]	0.04 (0.04 to 0.13), P=0.001	58.999, P<0.000	77.966
Sociodemographics	Urban/rural	6 [41 57 60 66 94 98]	0.10 (0.06 to 0.14), P<0.000	2.110, P=0.834	0.000
	Child age	15 [23 41 52 54 56 57 60 65 66 70 71 73 81 86 94]	0.07 (0.01 to 0.13), P=0.029	127.178, P<0.001	88.206

*Reported outcomes for two different subsamples.
HPV, human papillomavirus.

in the following domains: (1) healthcare provider—physician recommendation (r=0.46 (95% CI 0.34 to 0.56)) and parents' trust in healthcare providers (r=0.11 (95% CI 0.01 to 0.21)); (2) parental HPV vaccine decision-maker—mother as HPV vaccine decision-maker (vs both parents) (r=0.34 (95% CI 0.23 to 0.44)); (3) parent's vaccine beliefs, attitudes and intentions—intention to vaccinate child for HPV (r=0.31 (95% CI 0.17 to 0.43)), belief in vaccines in general (r=0.19 (95% CI 0.08 to 0.29)), perceived HPV vaccine benefits (r=0.17 (95% CI 0.10 to 0.24)) and anticipatory regret if child is not vaccinated (r=0.14 (95% CI 0.11 to 0.17)); (4) preventive healthcare utilisation for child—routine child preventive check-up, past 12 months (r=0.22 (95% CI 0.11 to 0.33)); (5) insurance/cost—health insurance coverage of HPV vaccination (r=0.16 (95% CI 0.04 to 0.29)); (6) parents' HPV risk history—parent history of HPV (r=0.16 (95% CI 0.06 to 0.25)), mother's history of having a Pap test (r=0.06 (95% CI 0.004 to 0.107)), parent history of genital warts (r=0.05 (95% CI 0.03 to 0.07)), parent or family member history of abnormal Pap smear (r=0.02 (95% CI 0.01 to 0.04)); (7) parents' HPV-related knowledge and awareness—HPV vaccine knowledge and awareness (r=0.14 (95% CI 0.05 to 0.23)) and cervical cancer/HPV knowledge (r=0.04 (95% CI 0.04 to 0.13)); and (8) sociodemographic factors—urban versus rural location (r=0.10 (95% CI 0.06 to 0.14)) and child's age (r=0.07 (95% CI 0.01 to 0.13)). Factors negatively associated with parents' uptake of HPV vaccines for their children were parents' vaccine attitudes—HPV vaccine safety concerns (r=−0.31 (95% CI −0.41 to −0.16)); and insurance/cost—out-of-pocket cost (r=−0.15 (95% CI −0.22 to −0.07)).

Between-study variability

The small number of studies examining some of the factors precluded us from conducting subanalyses to assess the impact of risk of bias on the findings for those outcomes; therefore, we examined individual results to identify potential reasons for between-study variability. We found high heterogeneity in the reported correlations between parents' HPV vaccine uptake for their children and the following factors: physician recommendation, intention to vaccinate child for HPV, HPV vaccine safety concerns, belief in vaccines in general, perceived HPV vaccine benefits, routine child preventive check-up, health insurance coverage of HPV vaccination, mother's history of receiving a Pap test, HPV vaccine knowledge and awareness, and child age. We found medium heterogeneity in cervical cancer/HPV knowledge, and low heterogeneity in parents' trust in healthcare provider, mother as HPV vaccine decision-maker (vs both parents), anticipatory regret, out-of-pocket cost for HPV vaccination, parent history of HPV, parent history of genital warts, parent or family history of abnormal Pap smear, and urban versus rural location.

Moderating factors of parents' uptake of HPV vaccines for children

We conducted moderation analyses to examine whether the variance in HPV vaccine uptake could be explained by three covariates—sex of child, sex of parent and study risk of bias—after adjusting for other factors (eg, physician recommendation, health insurance coverage, HPV vaccine safety concerns and others). We found that the omnibus test for the effect of sex of parent on uptake of HPV vaccines yielded Q=10.41, df=2 (P=0.006); thus, controlling for sex of child and risk of bias, there is some evidence that effect size for parents' uptake of HPV vaccines for their children may be related to the sex of the parent. More specifically, mothers/female guardians had a coefficient of −0.018, suggesting that uptake may be greater in studies that included mothers/female guardians as opposed to studies that included both mothers/female guardians and fathers/male guardians, controlling for sex of child and risk of bias. However, this model was not statistically significant (P=0.653).

The omnibus test for the effect of sex of child indicated Q=10.37, df=3 (P=0.016); therefore, controlling for sex of parent and risk of bias, there is some evidence that effect size for parents' uptake of HPV vaccines for their children is related to the sex of the child. More specifically, we found a significant effect for preadolescent and adolescent girls and HPV vaccine uptake. The coefficient for girls of 0.096 (P=0.036) indicates that parents' uptake of HPV vaccines for their children is greater in studies that included preadolescent and adolescent girls, as opposed to studies that included both preadolescent and adolescent girls and boys, controlling for sex of parent and risk of bias.

We found no significant moderating effect of study risk of bias on HPV vaccine uptake. The proportion of variance in uptake that is explained by all three covariates is 28%. The results of the various sensitivity analyses and examination of a funnel plot of the 62 studies included in the meta-analysis showed no publication bias (Begg and Mazumdar rank correlation, P=0.945).

DISCUSSION

This systematic review and meta-analysis is among the first to assess correlates of parents' HPV vaccine uptake for their children, rather than proxies such as HPV vaccine acceptability or intention to vaccinate. Results from 79 studies in 15 countries including over 840 000 parents indicate overall suboptimal parental uptake (41.5%) of one or more doses of HPV vaccines for their children. Notably, parents' HPV vaccine uptake differed significantly by sex of the child: uptake for girls (46.5%) and in mixed samples of girls and boys (39.8%) was higher than uptake for boys (20.3%), indicating substantial sex disparities in uptake.

Parents' overall modest levels of HPV vaccine uptake for their children more than a decade after the initial licensure of an HPV vaccine indicate the importance of synthesising evidence to support effective programmes to accelerate uptake. The disparities in uptake by sex of child are consistent with the later approval and recommendation of HPV vaccination for boys than girls in the USA, where the majority of studies were conducted, and the lack of coverage of HPV vaccination for boys in many other national insurance programmes.[101] However, our findings also suggest a number of enduring factors that may contribute to sex disparities in HPV vaccine uptake. A predominant policy focus in many national public health strategies and funding mechanisms on increasing HPV vaccine coverage among girls and young women in order to achieve herd protection may contribute to a lack of perceived benefits of HPV vaccination for men on the part of parents, healthcare providers and boys/young men themselves[101 102]—despite the documented effectiveness and substantial health benefits of HPV vaccination for boys.[9 36]

In line with previous descriptive reviews largely focused on uptake for girls,[12 103] physician recommendation had the single greatest effect on parents' uptake of HPV vaccines for their children, supported by evidence from over 20 studies. As the first meta-analysis of HPV vaccine uptake, to our knowledge, to test for the moderating influence of child's sex—and based on previous studies that suggest a tendency on the part of healthcare providers to offer HPV vaccine recommendations to those they perceive to be more likely to benefit from and to accept vaccination (ie, girls, patients with health insurance)[104]—this highlights the importance of physicians making recommendations for boys as well as girls in order to increase parents' HPV vaccine uptake for their children.[103 105] The vital role of physician recommendation of HPV vaccination for boys is further supported by the significant association (with evidence from 10 studies) of parents' perceived HPV vaccine benefits with their uptake of HPV vaccines for their children, in the context of the enduring perception that HPV is a woman's concern.[102]

Results from meta-analyses indicate a substantial negative effect of parents' concerns about HPV vaccine safety on HPV vaccine uptake for their children, as well as positive effects of belief in vaccines in general and perceived HPV vaccine benefits; each of these factors is supported by findings from 10 or more studies. These parental attitudes and beliefs about vaccines in general, and HPV vaccines in particular, may be strategic targets for both physician engagement with parents and for public health education campaigns in accelerating HPV vaccine uptake. Nevertheless, the broader phenomenon of vaccine hesitancy, evidenced in the USA[106] and other countries,[8] has resulted in parental resistance to childhood vaccinations, with a subsequent re-emergence of vaccine-preventable diseases in the USA.[106] In the context of even greater scrutiny that may be applied to an adolescent vaccine for a sexually transmitted infection,[8] the significant effects of parents' attitudes and beliefs support the importance of careful and respectful healthcare provider engagement with parents and their concerns as a facilitator of HPV vaccine uptake.[105 107] The positive impact of parents' trust in healthcare providers on their uptake of HPV vaccines for their children, as similarly identified in regard to childhood vaccines,[108] provides evidence to support the importance of the process of physician engagement in effectively communicating with parents.[105 107 109] Findings from this review suggest a substantive focus on addressing parents' HPV vaccine safety concerns and supporting their positive beliefs in the health benefits of vaccines in general, as well as explaining the particular benefits of HPV vaccines for their children, including boys and girls.

Routine child preventive check-up was identified across eight studies as being positively associated with parents' HPV vaccine uptake for their children. It may be that the public health focus on routine gynaecological cancer screening in preventive care for women, with no analogously effective screening mechanism available for anal or oropharyngeal cancer among men, may thereby contribute to sex disparities in HPV vaccine uptake. This supports the importance of reducing missed opportunities in encounters with healthcare providers to promote HPV vaccine uptake for boys.[103]

Beyond healthcare provider-related factors and parents' attitudes and beliefs about vaccines, the significant impact of health insurance coverage of HPV vaccination and out-of-pocket cost on parents' uptake of HPV vaccines for their children supports the important role of healthcare policy and funding in promoting HPV vaccine uptake.[11 101] We also identified a small but significant effect of urban versus rural location on HPV vaccine uptake. These correlates of uptake underscore the importance of structural interventions, such as the US Vaccines for Children programme which provides vaccines at no cost to low-income children, and school-based HPV vaccine delivery programmes, such as in Australia (including boys and girls), which have helped to reduce disparities in uptake by children's race/ethnicity, sex and socioeconomic status.[110] They also suggest addressing rurality as a sociodemographic factor that may contribute to disparities in HPV vaccine uptake.

Methodological considerations

Several methodological issues pose limitations to this review, including the dearth of intervention studies, high risk of bias in the majority of studies reviewed and heterogeneity due to between-study variability. Some variables were meta-analysed across relatively few studies precluding subanalyses of moderator variables, or meta-regression, to assess the impact of risk of bias on the findings. However, we used random-effects models to account for methodological variability, assessed each study for risk of bias, assessed risk of bias as a moderator and calculated accepted statistical indices to assess heterogeneity, in accordance with PRISMA[15] and MOOSE guidelines.[16] Additionally, 10 of the 19 factors in meta-analyses were supported by findings from at least six or more studies, with six factors supported by findings from 10 or more studies.

An additional limitation is that the vast majority of studies focused on mothers, with very few studies assessing fathers' HPV vaccine uptake for their children,[90 98] and several failing to indicate the sex of the parent surveyed. Future studies should examine fathers' uptake of HPV vaccines for their children, with parents' uptake disaggregated by sex, and assess whether fathers' support for HPV vaccination of their daughters and/or sons differs from that of mothers. Similarly, while nearly all studies reported ages of the children vaccinated, over a quarter did not report parents' age(s) and many studies failed to include basic descriptive statistics on parents' age (ie, mean or median, range). As many studies did not identify the type of physician who recommended HPV vaccination, future investigations should specify physician and healthcare provider type to assess differences among providers and specific practice implications. Understandably, some of the missing demographic data may be a result of limitations in national and regional immunisation registries; augmenting the information collected in these databases may provide further evidence to inform tailored interventions to increase parents' HPV vaccine uptake for their children.

Finally, parents' uptake of HPV vaccines for their children may be affected by a reduction in the required number of doses to achieve full protection, as well as broad structural and social factors, including high-income versus low-income countries, public funding of HPV vaccination for girls and for boys, school-based versus clinic-based vaccination, HPV prevalence, and cultural differences. As we used HPV vaccine initiation as the primary outcome based on data reported in more than 90% of the studies reviewed, the same factors are likely to be associated with initiation of a two-dose regimen; the latter may help to mitigate to an extent the negative effects of out-of-pocket costs and perhaps parents' safety concerns on uptake. We compared uptake in high-income versus low-income and middle-income countries; however, the paucity of studies in the latter context, including demonstration projects that may overestimate broader population uptake, may have limited statistical power to detect differences, and we were unable to systematically model other social-structural factors in this meta-analysis. Nevertheless, the significant effects of health insurance coverage and out-of-pocket cost on parents' uptake of HPV vaccines for their children indicate the impact of national policies and funding mechanisms in the USA—where 9vHPV is now largely a standard of care for insurance companies—and other countries (with only 6% including HPV vaccines for boys in national immunisation programmes vs 37% for girls only).[9] It is also crucial to expand investigations in low-income and middle-income countries, with the highest morbidity due to HPV-related cancers and the lowest access to and uptake of HPV vaccines.[8]

This systematic review and meta-analysis indicates overall suboptimal parental uptake of HPV vaccines for their children across 79 studies conducted in 15 countries, along with significant correlates of uptake at the level of healthcare providers, parental attitudes, beliefs and knowledge, and structural factors such as insurance coverage and out-of-pocket cost. Given the vital role of parents in HPV vaccine uptake for their children, public health strategies should address modifiable factors across multilevel domains that influence parents' uptake. In particular, a focus on increasing provider, especially family physician,[74] recommendation of HPV vaccines to parents of boys as well as girls, including during routine healthcare visits, may reduce sex disparities in HPV vaccine uptake and contribute to accelerating uptake overall.[14] Further research including intervention studies and longitudinal designs, with results disaggregated by sex of children and parents, and by HPV vaccine initiation versus series (now two-dose) completion, is needed to advance evidence of factors associated with parents' uptake of HPV vaccines for their children. Evidence-informed strategies that contribute to accelerating HPV vaccine uptake are critical to realising the full public health potential of HPV vaccines on cancer prevention.

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Contributors PAN had full access to all of the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis. PAN conceptualised and designed the study, contributed to data analysis and interpretation, drafted the initial and final manuscript, provided funding support, and supervised study implementation. CHL contributed to study conceptualisation and design, led and supervised statistical analysis, and critically reviewed the manuscript. AL-D led article screening, data extraction and assessment of risk of bias, contributed to data analysis and drafting the manuscript, and provided administrative support. PB contributed to article screening, data extraction, risk of bias assessment, statistical analysis and revision of the manuscript. ST, CR, ND and FA contributed to article screening, data extraction and risk of bias assessment, and reviewed the manuscript.

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