

Title page

Which interventions improve HPV vaccination uptake and intention in children, adolescents and young adults? An umbrella review

Clare Bennett^{1,2}

Deborah Edwards¹

Susan M Sherman³

Peter Baker⁴

Dur-e-Nayab Waheed⁵

Alex Vorsters⁵

Hüsna Sarıca Çevik⁶

Emilie Karafillakis⁷

Gillian Prue⁸

Daniel Kelly^{2,4}

1. Wales Centre for Evidence Based Care, School of Healthcare Sciences, College of Biomedical and Life Sciences, Cardiff University, Cardiff, UK
2. School of Healthcare Sciences, College of Biomedical and Life Sciences, Cardiff University, Cardiff, UK
3. School of Psychology, Keele University, Keele, UK
4. European Cancer Organisation, Brussels, Belgium
5. Centre for the Evaluation of Vaccination, Faculty of Medicine and Health Sciences, University of Antwerp, Belgium
6. Çankaya District Health Directorate, Ankara, Turkey
7. Faculty of Epidemiology and Population Health, Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK
8. School of Nursing and Midwifery, Queens University Belfast, Northern Ireland, UK

Corresponding author

Dr Clare Bennett
School of Healthcare Sciences
College of Biomedical and Life Sciences
Cardiff University
Room 3.26, Tŷ Dewi Sant
Heath Park, Cardiff, CF14 4XN
Email: BennettCL3@cardiff.ac.uk

Funding

This research was co-ordinated by the European Cancer Organisation, who received some financial contributions towards its cost from Community 365 charity and healthcare industry partners: NOMAN, BD, MSD and Roche.

Word count 3517 (excluding title page, abstract, references, figures and tables)

KEYWORDS

Review; interventions; HPV; HPV vaccination uptake; children; adolescents; young adults; quantitative; effectiveness; coverage

ABSTRACT

Background

Human papillomavirus (HPV) vaccination offers protection against the virus responsible for cervical, oropharyngeal, anal, vulval and penile cancers. However, there is considerable variation across, and even within, countries as to how HPV vaccination is offered and accepted. This review aimed to identify what interventions exist to promote uptake and how effective they are.

Methods

We conducted an umbrella review using the JBI methodology to evaluate routine or catch-up interventions to increase HPV vaccination uptake and/or intention for children aged nine years and older, adolescents and young adults up to 26. Comprehensive searches for English language quantitative systematic reviews, published between January 2011 to July 2021, were conducted across five databases. After reviewing titles and abstract, relevant papers were independently assessed in detail.

Main results

From 1046 records identified, 10 articles were included in the review. They reported on 95 RCTs, 28 quasi-experimental studies, 14 cohort studies, six non-randomized pre-test/post-test studies with control groups, five single group pre-test/post-test studies, one single group post-test study and one randomised longitudinal study. Some interventions promoted change at the individual, community or organisational level, whilst others used a multi-component approach. Face to face presentations, printed information and supplementing both strategies with additional components appear effective at increasing vaccination intention, while reminders and multi-component strategies, especially ones that include some intervention aimed at provider level, appear effective at increasing vaccination uptake. Interventions that did not lead to an improvement in HPV vaccination intention or uptake varied in design and impacts were inconsistent across children/adolescents, young adults or parents.

Conclusions

The evidence suggests that there is no single solution to increasing vaccination uptake and that different approaches may be better suited to certain populations. However, generalisations are limited by poor reporting and a paucity of studies beyond the USA. Further high-quality studies, therefore, are needed to understand how best to increase HPV vaccination uptake in different target populations.

Key messages

What is already known about this topic?

- Elimination of HPV is possible through HPV vaccination.

What this study adds:

- This is the first umbrella review to explore the evidence for interventions used to improve HPV vaccination intention and uptake in children, adolescents and young adults. We found no single solution to increasing vaccination uptake but suggest that specific approaches may be more suited to some populations than others. Face to face presentations, printed information and supplementing both strategies with additional components appear effective at increasing vaccination intention and reminders and multi-component strategies, especially ones that include some intervention aimed at provider level, appear effective at increasing vaccination uptake.

Implications:

- Further high-quality research is needed to understand how best to increase HPV vaccination uptake in different populations, as well as in countries where vaccine availability may be limited.

INTRODUCTION

There are approximately 200 different types of HPV,¹ with types 16 and 18 being estimated to cause around 5% of all cancers worldwide.² The virus is implicated in virtually all cases of cervical cancer, almost 90% of anal cancers and a significant proportion of oropharyngeal, penile, vaginal and vulval cancers.³ Approximately 20% of HPV cancer cases occur in men, although one study suggests the proportion could be closer to 30%.⁴

The overwhelming majority of cancers caused by HPV can be prevented by vaccination, ideally administered in early adolescence. A large-scale study of women in England found that the HPV immunisation programme has ‘successfully almost eliminated’ cervical cancer, especially in individuals who were offered the vaccine at age 12–13 years.⁵ However, it is increasingly accepted that gender-neutral HPV vaccination programmes are central to efforts to eliminate all cancers caused by HPV,⁶ as recognised in Europe’s Beating Cancer Plan, 2021.⁷

Elimination of HPV is possible if 80% coverage in girls and boys is reached and if high vaccine efficacy is maintained over time.⁸ Most countries do not reach that threshold⁹ with ‘vaccine hesitancy’ being a key barrier.¹⁰ This makes it critically important to understand factors that promote the uptake of HPV vaccination. There is also a need to identify the effectiveness of evidence-based interventions aimed at highlighting constituent elements of successful interventions that can be recommended, or indeed strengthened, for different target populations. This project aimed to identify interventions by drawing on existing systematic reviews that have collated the available published evidence, and to use this to highlight approaches that might be most successful in increasing HPV vaccination uptake and intention in children, adolescents and young adults. To date no other umbrella reviews have been conducted in this area. The aim of this umbrella review was, therefore, to answer the question “What is the evidence for interventions used to improve HPV vaccination uptake in children, adolescents and young adults?” The specific objectives were to provide an overview of interventions used to improve HPV vaccination uptake and intention and to summarise their effectiveness. A modified version of the social ecological model was used throughout, as a framework for considering the various interventions.¹¹

METHODS

This umbrella review used the JBI methodology for umbrella reviews,¹² following the study protocol which was registered with PROSPERO (CRD42021273894).¹³

Inclusion criteria

This review considered systematic reviews of quantitative studies (randomized controlled trials (RCTs), quasi-experimental, and pre-post design) that evaluated routine or catch-up interventions aimed at increasing HPV vaccination coverage in nine- to 26-year-olds or to promote acceptability among parents/guardians. Uptake of the HPV vaccination (initiation, completion, receipt of any dose) was considered the primary outcome. The secondary outcome was intent.

Search strategy

Comprehensive searches (Supplementary File 1) for English language systematic reviews were conducted across five databases: MEDLINE, Embase, Global Health, CINAHL and Web of Science, from January 2011 to July 2021. Hand searching and forward citation tracking were also conducted.

Study screening, selection and assessment of methodological quality

All citation titles and abstracts were screened independently by two reviewers from the review team (CB, DE, SMS, DW, AV, HSC, EK, GP) and considered against topic inclusion criteria. All relevant papers were retrieved in full and assessed against the inclusion criteria independently by two reviewers, using a purposely designed screening tool. Eligible systematic reviews were appraised independently by two reviewers for methodological quality using the standardized JBI critical appraisal instrument.¹² Throughout, disagreements were resolved through discussion, or with a third reviewer. All reviews, regardless of their methodological quality, underwent data extraction and synthesis.

Data extraction

Demographic data (Supplementary Files 2 and 3) and outcome data (Supplementary Files 4-8) were extracted directly into tables with one reviewer from the team extracting the data, and a second checking independently for accuracy and completeness.

Data summary

Due to the heterogeneity of the individual interventions an overall meta-analysis of effect estimates was not possible. Additionally, due to the poor reporting of summary statistics we were unable to produce a standardised metric across the individual findings across these systematic reviews.¹⁴ The majority of primary studies presented in the included systematic reviews only reported the direction of effect and there was wide inconsistency in the effect measures and/or data reported across studies. The synthesis method chosen was therefore based on vote counting, underpinned by the direction of effect or statistical significance.¹⁵ The evidence of effect across the studies within each review were presented in tables (Supplementary File 4-8) and reported narratively as a series of thematic summaries¹⁶ first by participant group, and then by effectiveness of interventions across different outcomes. To organise effective interventions in a meaningful way a version^{17,18} of the social ecological model¹¹ was employed to identify whether HPV vaccination interventions were targeted at individual, community and organisational levels.

Flow of studies through the review

The search strategy identified 1046 records. After removal of duplicates, initial screening and eligibility assessment, 10 systematic reviews were considered suitable for inclusion. The PRISMA checklist was followed for the reporting of this review. The flow of studies through the review is presented in a PRISMA flow diagram (Figure 1).¹⁹ Excluded studies are detailed in Supplementary File 9. All reviews underwent critical appraisal (Table 1) and were considered suitable for inclusion.

[INSERT FIGURE 1 AROUND HERE]

Methodological quality

The results of the critical appraisal are summarized in Table 1. Methodological quality was difficult to ascertain in relation to assessment of publication bias and the conduct of critical appraisal due to limitations in reporting.

Table 1: Critical appraisal scores

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11
Abdullahi et al. 2020 ²⁰	Y	Y	Y	Y	Y	Y	Y	N	UC	N/A	Y
Barnard et al. 2019 ²¹	Y	Y	Y	Y	Y	N	UC	Y	UC	UC	Y
Eisenhauer et al. 2021 ²²	Y	Y	Y	Y	Y	UC	Y	N	UC	Y	Y
Flood et al. 2020 ²³	Y	Y	Y	Y	Y	Y	Y	UC	UC	Y	Y
Fu et al. 2014 ²⁴	Y	Y	Y	Y	Y	UC	Y	Y	UC	Y	Y
Ilozumba et al.2021 ²⁵	Y	Y	Y	Y	Y	Y	Y	Y	UC	N/A	Y
Lott et al. 2020 ²⁶	Y	Y	Y	Y	Y	UC	Y	Y	UC	N/A	Y
Mogaka et al. 2021 ²⁷	Y	Y	Y	Y	Y	Y	Y	Y	UC	N	Y
Priest and Knowlden 2015 ²⁸	Y	Y	Y	Y	Y	UC	Y	Y	UC	N/A	Y
Rodriguez et al. 2019 ²⁹	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y

Key: N/A: not applicable, N: No, UC: unclear, Y: Yes
 Q1 Is the review question clearly and explicitly stated?
 Q2 Were the inclusion criteria appropriate for the review question?
 Q3 Was the search strategy appropriate?
 Q4 Were the sources and resources used to search for studies adequate?
 Q5 Were the criteria for appraising studies appropriate?
 Q6 Was critical appraisal conducted by two or more reviewers independently?
 Q7 Were there methods to minimize errors in data extraction?
 Q8 Were the methods used to combine studies appropriate?
 Q9 Was the likelihood of publication bias assessed?
 Q10 Were recommendations for policy and/or practice supported by the reported data?
 Q11 Were the specific directives for new research appropriate?

FINDINGS OF THE REVIEW

Characteristics of included systematic reviews

Across the 10 systematic reviews, 110 unique primary studies were included. The corrected covered area³⁰ was 4%, meaning that there was a slight overlap (n=31) of primary studies duplicated across all systematic reviews. Allowing for this, the reviews included: 95 RCTs, 28 quasi experimental studies, 14 cohort studies, six non-randomized pre-test / post-test studies with control groups, five single group pre-test / post-test studies, one single group post-test study and one randomised longitudinal study. Primary studies were published between 2004 and 2020. A variety of methods of analysis were conducted with narrative synthesis being the most common (n=6).^{21,23,25-28}

Most of the included primary studies in the systematic reviews were conducted in the USA.^{20–29} Other countries that were represented were Australia (n=5),^{21,23–25,28} the UK, (n=3)^{20,23,24} Sweden (n=3),^{20,23,24} India (n=2),^{24,27} Canada (n=1),²⁸ China (n=1),²⁷ Hong Kong (n=2),^{23,24} Hungary (n=1),²³ Ireland (n=1),²⁴ Singapore (n=1),²³ Tanzania (n=1),²⁰ and Taiwan (n=1).²³ Two reviews only included studies from the USA.^{22,29} The total number of participants across all ten systematic reviews was 451,132 and the number of participants in each systematic review ranged from 2625²¹ to 276,205²² with all reviews, except one²² including studies with small sample sizes of less than 200 participants. Five systematic reviews did not report the ethnicity of participants^{20,21,23,27,28} and in one further systematic review, 28 of the 30 included studies did not report on ethnicity.²⁹ For the remaining systematic reviews, populations were either predominately white (n=2)^{22,24} or included a broad range of ethnicities.^{25,26}

The outcomes included within the systematic reviews were HPV vaccination uptake rates (n=9)^{20–29} and/or HPV vaccination intention (n=6).^{23–28} The terminology used to describe the outcome measures for HPV vaccination uptake varied. We adopted the authors' original language by reporting on HPV Vaccination series 'initiation', 'completion' or 'uptake' rates. In this umbrella review the rate of HPV vaccination intentions ranged from 24% pre-intervention to 90% post-intervention. The baseline vaccination coverage rates reported within individual studies varied greatly and, where reported, ranged from 1% to 53%.

Types and effectiveness of interventions

Numerous and varied interventions were reported across the systematic reviews. Interventions that focused on change at the level of the individual included a range of educational, promotional nudge based, reminder-based and incentive-based strategies. There was wide variation across the timing, duration and nature of educational interventions. For example ranging from shorter presentations (3–13 minutes,^{20,24,27} a 5 minute radio broadcast,²⁷ 30–40 minutes²⁰ or 1–2 hours presentations) to longer 2-3 day curriculum sessions²⁰ or 6-8 educational visits over 12 months.²⁰ Some systematic reviews did not report the duration of interventions that included videos or direct education.^{21,26,29} Others only reported that the timing and frequency of reminder messages varied widely.^{22,25} Two different types of

interventions focused on change at the level of the community and included radio features and public health strategies. Radio features included advertisements or announcements,^{24,27} in some instances also with message framing²⁴. Public health strategies included school-based vaccination programmes, a practice based “vaccine blitz”, vaccine walk-in clinics and express clinics.^{22,29} There were several different types of provider-orientated interventions that focused on change at the organisational level. These included continuing professional education, electronic health record alerts, a vaccination coordinator post, home visits, health information technology systems, nurse standing orders and pre-typed consents.^{22,29}

The effectiveness of interventions for HPV vaccination intention and HPV vaccination uptake are presented by participant group i.e., children and adolescents, parents/guardians, and young adults. The findings for young adults are based on studies that recruited from education, community settings, or both. The majority of studies that focused on HPV vaccination intent did not involve any follow-up assessment beyond the period immediately following the intervention. Where reported the period of follow-up for reporting outcomes for studies that focused on HPV vaccination uptake varied from 4 weeks^{21,26,28} to 12 months.^{20,26}

Effectiveness of interventions aimed at children and adolescents (intention)

Interventions from nine studies reported across three systematic reviews^{23,24,27} investigated HPV vaccination intention in children and adolescents. They used a variety of educational strategies targeted at the individual level, and all but one showed significant positive effect on HPV vaccination intention. Interventions that appeared to be effective included educational strategies employing face-to-face presentations (talks or slideshows),^{23,27} face to face presentations plus printed information²³ or Facebook discussions,²³ printed information,^{23,24} technology-mediated presentations (videos²⁴ or iPads²³) and technology-mediated presentations (videos) plus printed information.²⁴ An educational strategy using technology-mediated presentations to deliver a photographic short story²⁷ did not appear to improve HPV vaccination intention.

Effectiveness of interventions aimed at parents (intention)

Interventions from 15 studies across four systematic reviews^{24–27} investigated parental HPV vaccination intention. These were all delivered in community settings and used a variety of educational strategies. Interventions that appeared to be effective included educational strategies using face-to-face presentations (slideshows)^{24,27} and printed information plus Q&A sessions.^{24,27} There were mixed findings in relation to technology-mediated presentations, for example videos^{26,27} were successful but iPads²⁵ were not, and printed information had variable results, with^{24,27} or without^{24,27} message framing. Educational strategies involving radio features^{24,27} and online information with message framing²⁴ did not appear to improve HPV vaccination intention.

Effectiveness of interventions aimed at young adults (intention)





Interventions from 15 studies across four systematic reviews^{24–26,28} investigated parental HPV vaccination intention. These were delivered in community settings and used a variety of educational strategies. Interventions that were effective included educational strategies using face-to-face presentations (slideshows²⁴); face-to-face presentations plus a theory-based slideshow,²⁸ discussion²⁸ or role play,²⁸ printed information plus Q&A sessions²⁴ or quizzes²⁴ and text-based health education.²⁵ There were mixed findings regarding technology-mediated presentations^{24,25,28} printed information (with²⁴ or without message framing^{24,28}) and online information with message framing.²⁴ Educational strategies employing radio features with message framing,²⁴ and technology-mediated presentations of culturally-appropriate storytelling to specific ethnic groups²⁶ did not appear to improve HPV vaccination intention.

[INSERT TABLE 2 AROUND HERE]

Table 2: Summary of evidence for the effectiveness of interventions for HPV vaccination intention

Interventions	Intention		
	Children or Adolescents	Parents	Young adults
EDUCATIONAL			
Printed Information	23,24	24,27	24,28
Printed information with message framing		24,27	24
Printed information plus		24,27	24
Technology-mediated presentation - IPad or Video	23,24	25 26,27	24,25,28
Technology-mediated presentation - Stories	27		26
Technology-mediated presentation plus	24		
Face to face presentation	23,27	24,27	24
Face to face presentation plus	23		28
Text based information			25
Online information with message framing		24,27	24
Radio features		24	
Radio features with message framing			24

Key: 'Plus' refers to a range of additional components

-  Intervention leads to improvement in HPV vaccination intention
-  Intervention does not lead to an improvement in HPV vaccination intention
-  Intervention does not consistently lead to an improvement in HPV vaccination intention (some studies showing improvement and others not)
-  Not reported

[INSERT FIGURE 2 AROUND HERE]

Effectiveness of interventions aimed at children, adolescents and parents (uptake)

Interventions conducted with children, adolescents and parents from 17 studies reported across six systematic reviews^{20,22,24–26,29} investigated 'HPV vaccination initiation rates' and used educational, reminder or multi-component strategies. These were targeted at individuals, organisational and individual level, or community and organisational level. Ten studies showed significant positive effects of interventions on HPV vaccination initiation rates. Interventions that appeared to be effective included educational strategies (no further details provided²⁹), provider orientated strategies (continued professional education)²⁰ and multi-component interventions that involved a variety of provider-orientated strategies.^{22,29} Multi-component interventions involving an educational component alongside reminder^{22,26,29} and/or incentive^{20,22,24–26,29} strategies and stand-alone reminder strategies^{22,29} had mixed results. Multi-

component interventions involving education, reminders and/or incentives conducted with mothers^{26,29} or mother/daughter dyads^{20,26} and a multi-component intervention with a promotional nudge (a keychain)^{20,26} did not appear to improve HPV vaccination initiation rates.

Interventions from 22 studies reported across six reviews^{20,22,23,25,26,29} investigated 'HPV vaccination completion rates' and used educational, reminder-based or multi-component strategies targeted at individual or organisational and individual levels. Eighteen studies^{20,22,23,25,26,29} showed a significant positive effect of the intervention on HPV vaccination completion rates. Interventions that appeared to be effective included stand-alone reminder-based strategies,^{22,23} educational strategies²⁹ (no further details provided), multi-component interventions that involved provider-orientated strategies,^{22,29} with the exception of one intervention which involved provider education and sensory rewards (incentive) in the form of a 'HPV gong' which participants could strike or a 'HPV puppy' which participants could interactive with.²² Stand-alone reminder-based strategies included text messages,^{22,23} telephone calls,^{22,23} pre-recorded voice messages^{22,23} or postcards.^{22,23} Where evaluated, text messages were more effective than other methods.^{22,23} Multi-component interventions that involved an educational component alongside reminder^{25,26,29} or incentive strategies^{20,25,26,29} had mixed results.

Interventions from 13 studies reported across four systematic reviews^{20,23,25,29} investigated 'HPV vaccination uptake rates' and used educational, organisational, public health, reminder-based or multi-component strategies, targeted at either the individual level, organisational level, organisational and individual levels or community and individual levels. All studies except one showed significant positive effects of interventions on HPV vaccination uptake rates. Interventions that appeared to be effective included educational strategies²⁹ (no further details provided), educational strategies involving face to face presentations (a talk^{20,23}), technology-mediated presentations (iPad²⁵), stand-alone reminder-based strategies,^{25,29} public health strategies (a school-based vaccination clinic²⁹) and multi-component interventions strategies (public health, education and radio features;²⁰ education, reminders, incentives or all²⁰ and provider-orientated interventions with reminders^{20,29}). Stand-alone reminder-based strategies included text messages,^{25,29} telephone calls²⁵ or

mailed reminders.²⁵ Where evaluated, text messages were more effective than other methods.²⁵ Face-to face presentations plus a range of classroom-based activities²³ did not appear to be effective in improving HPV vaccination uptake rates.

Effectiveness of interventions conducted with young adults (uptake)

Interventions from 10 studies reported across four systematic reviews^{21,25,26,29} investigated 'HPV vaccination initiation rates' and used educational, public incentive-based, reminder-based or multi-component strategies which were targeted at the individual level. Nine studies showed significant positive effects of interventions on HPV vaccination initiation rates. Interventions that appeared to be effective included reminder-based strategies (text messages^{20,25,26}), incentive-based strategies (where the vaccine was provided free of charge (USA)²⁹ and/or included a \$25 gift voucher²⁹) and multi-component interventions that involved an educational component alongside a reminder-based strategy.²⁶ Educational interventions that involved online information^{21,29} and technology-mediated presentations^{21,26} did not appear to improve HPV vaccination initiation rates.

Interventions from nine studies reported across six systematic reviews^{20,21,24,25,27,29} investigated 'HPV vaccination completion rates' and used educational, reminder-based, incentive-based studies or multi-component strategies which were targeted at the individual level. Seven studies showed significant positive effects of intervention on HPV vaccination completion rates. Interventions that appeared effective included reminder-based strategies (using texts,^{25,29} telephone messages,^{25,29} mail,^{25,29} email,^{25,29} Facebook messages^{25,29}) and incentive-based strategies (where the vaccine was provided of free of charge in the USA²⁹). Multi-component interventions involving an educational component alongside a reminder²⁶ or incentive-based strategy^{24,27} had mixed results. Educational strategies (online information^{21,29}) did not appear to improve HPV vaccination initiation rates.

Interventions from seven studies reported across six systematic reviews.^{21,24–27,29} investigated 'HPV vaccination uptake rates' and used educational, reminder-based, incentive-based studies or multi component strategies which were targeted at the individual level. Only two studies showed significant positive effects of interventions on HPV vaccination uptake rates. The intervention that appeared to be effective was

language-specific peer-to-peer education to Chinese students at a USA university.^{24–29} Multi-component interventions that involved an educational component alongside a reminder^{21,24–26,28,29} did not appear to improve HPV vaccination uptake rates. Educational interventions involving technology-mediated presentations, with²² or without²² message framing, had mixed results. However, when video narratives were led by peers and medical experts,^{21,24,28,29} vaccination uptake significantly improved. Educational components that only used printed information were not successful.²⁴

[INSERT TABLE 3 AROUND HERE]

Table 3: Summary of evidence for the effectiveness of interventions for HPV vaccination uptake

Interventions	Outcomes					
	Initiation (Dose 1)		Completion (Dose 3)		Uptake	
	CA & P	YA	CA & P	YA	CA & P	YA
EDUCATIONAL						
Educational (further details not provided)	29		29		29	
Printed Information						24
Printed information with message framing						
Printed information plus						
Technology-mediated presentation - iPad or Video					25	22
Technology-mediated presentation - Video with message framing		21,26				22
Technology-mediated presentation - Stories		21,26				
Technology-mediated presentation plus						
Face to face presentation					20,23	24–29
Face to face presentation plus					23	
Text based information						
Online information		21,29		21,29		
REMINDER-BASED						
Text messages	22,29	20,25,26	22,23	25,29	25,29	
Telephone calls	22,29		22,23	25,29	25	
Mail	22,29		22,23	25,29	25	
Email				25,29		
Facebook message				25,29		
INCENTIVE-BASED						
Vaccine free of charge		29		29		
PROVIDER-ORIENTATED INTERVENTION						
Continuing professional education	20					
MULTI-COMPONENT						
Educational and promotional nudge	20,26		20,26			
Educational and reminders, incentives or both	20,22,24–26,29	26		24,26,27	20	21,24–26,28,29
Reminders and incentives			22,26			

Provider-orientated intervention and reminders, education or both	22,29		22,29		20,29	
Provider-orientated intervention and incentive	22,29		22			
Provider-orientated intervention and public health intervention	22,29		22,29			
Public health intervention, education and radio features					20	
PUBLIC HEALTH						
School based vaccination clinics					29	

Key: CA = Children or Adolescents, P = Parents, YA = Young Adults

- Intervention leads to improvement in HPV vaccination uptake
- Intervention does not lead to an improvement in HPV vaccination uptake
- Intervention does not consistently lead to an improvement in HPV vaccination uptake (some studies showing improvement and others not)
- Not reported

[INSERT FIGURE 3 AROUND HERE]

Certainty of the evidence

Supplementary Files (4-8) report the effect sizes for the investigated effects. However, only one of the included reviews completed the assessment of the certainty of the evidence using the GRADE approach²⁰ (which reported low to moderate certainty evidence). An overall assessment of the certainty of the evidence for each outcome of relevance was, therefore, not possible.

DISCUSSION

HPV vaccination intention

Our findings concur with those from previous reviews that rates of personal intentions to receive the HPV vaccine vary substantially.³¹ In some cases pre-intervention rates were as low as 24% which is lower than previously reported (48%).³¹ This was dependent on whether the target was parental intent for a child, or for individuals themselves. We found systematic reviews exploring vaccination intent that included educational interventions focused on change at the individual level. Factors related to intervention design that increased intention including timings, duration and delivery methods were also identified. It appears that educational interventions targeted at children and adolescents, as well as parents, are more successful than those targeted solely at parents.^{20,24,26}

HPV vaccination uptake

Impact interventions are context-specific. Percentage changes to HPV vaccination initiation and/or completion across studies was often unreported. A recent survey in the WHO European region demonstrated that only ten countries in this region have a defined target vaccine coverage rate for HPV vaccination. In addition, only four report target vaccination coverage rates in line with the WHO elimination goals.³² This is relevant since baseline coverage determines potential impact of an intervention. For example, one intervention that increases coverage from 30% to 60% in a particular context may not achieve similar coverage elsewhere, even in the same population, because the needs of sub-populations differ. Indeed, it has been reported that countries starting with suboptimal HPV vaccination coverage during the first two years of implementation are unable to increase coverage during subsequent years.⁹ Although specific interventions can be helpful, impact may be limited especially if trust in vaccines is low.^{33,34} Importantly, intention and uptake only become relevant when HPV vaccines exist, and are available and affordable. It is known that some low and middle income countries (LMICs) lack availability and different factors are, therefore, important in first promoting their availability at the level of national public health policy, and then to ensure that uptake is promoted in a culturally acceptable way.³⁵ The findings presented in a recent meta-analysis have identified the specific opportunities and challenges in achieving and maintaining high uptake of the vaccine in LMICs, and in securing sustainable funds for an HPV vaccine programme.³⁶

Influencing factors

Eisenhauer et al. (2021) suggested that “unmodifiable demographic variables” could contribute to a person’s decision to vaccinate.²² These include age, sex, race, setting and insurance coverage. However, only one of the included systematic reviews explored the influence of race/ethnicity on uptake and two further systematic reviews presented findings separately for gender.^{20,29} As with educational interventions aimed at improving vaccination intention, influencing factors for interventions aimed at improving uptake were related to intervention design including timing, duration and delivery methods or sources.

Multi-component strategies

Provider-orientated interventions (such as professional education, electronic health record alerts, a vaccination coordinator post, home visits, health information

technology systems, nurse standing orders and pre-typed consents) with the additional components of reminder-based strategies and/or incentive-based strategies and/or education strategies appeared effective. Also, public health interventions with the additional components of education, radio features and reminder and/or incentive-based strategies appeared to be effective. These findings concur with the work of Fernandez et al. (2010) suggesting that multi-component strategies, impacting across all levels of the social-ecological model, are likely to be most effective in increasing HPV vaccination uptake.³¹

Limitations of the evidence base

The generalisability of the findings from this umbrella review is limited by the high prevalence of studies from the USA. For all but one of the systematic reviews, more than half of included studies were from the USA (range 54% to 100%),²³ with three reviews exclusively including studies from there.^{22,26,29} This will limit applicability to the global stage, especially to LMICs.³⁵ There was a range of methodological concerns in the included systematic reviews including small sample sizes, poor and/or incorrect reporting of statistical analyses in the primary studies and inappropriate combining of studies in meta-analyses. Importantly, the primary outcome across most studies was self-reported vaccination behaviour as opposed to actual vaccination behaviour and vaccination intent was often used as a proxy for vaccination receipt. In addition, few studies examined impact of interventions on vaccination uptake in male students or across different ethnic groups. It is worth noting that very few studies within these systematic reviews provided details of theoretical models used to guide the planning and development of interventions. Similarly, service models needed to drive effective HPV delivery, alongside effective screening programmes were not explored. HPV vaccination uptake remains open to further research, as does the future impact of COVID-19 on vaccination awareness generally, and the key relationship between public health campaigns, social media activity and HPV cancer prevention.^{34,37}

CONCLUSION

Whilst no single solution to increasing HPV vaccination uptake or intention exists, this umbrella review has revealed a broad evidence base on which interventions can be designed and future researchers can build. Inconsistencies and gaps in reporting of systematic reviews, as well as limited geographical spread, means that these findings should be interpreted with caution.

Acknowledgments

This article is based on a report³⁸ entitled “Improving HPV Vaccine Uptake in Children, Adolescents, and Young Adults: An Umbrella Review of Interventions” published online at <https://www.europecancer.org/resources/255:hpv-vaccine-uptake> in April 2022 by The European Cancer Organisation. The authors are grateful to their respective universities for supporting this project.

Competing Interests

None declared

Funding

This research was co-ordinated by the European Cancer Organisation, who received some financial contributions towards its cost from Community 365 charity and healthcare industry partners: NOMAN, BD, MSD and Roche.

Contributorship Statement

DK was responsible for the conceptualisation of this project. The conduct of the umbrella review was led by DE and CB, with DE, CB, SS, DW, AV, HC, EK and GP conducting the screening, quality assessment, data extraction and narrative that underpinned this paper. All members of the team contributed to the reporting of the review. All authors edited and approved the final manuscript.

Figure legends:

Figure 1: Flow of studies through the review

Figure 2: Logic model of effective interventions for HPV vaccination intentions

Figure 3: Logic model of effective interventions for HPV vaccination uptake

REFERENCES

1. Hampson LN, Oliver AW, Hampson L. Potential effects of human papillomavirus type substitution, superinfection exclusion and latency on the efficacy of the current L1 prophylactic vaccines. *Viruses* 2020; 13: 22.
2. de Martel C, Plummer M, Vignat J, et al. Worldwide burden of cancer attributable to HPV by site, country and HPV type. *Int J Cancer* 2017; 141: 664–70.
3. Chaturvedi AK. Beyond cervical cancer: burden of other HPV-related cancers among men and women. *J Adolesc Health* 2010; 46: S20-6.
4. Hartwig S, Syrjänen S, Dominiak-Felden G, et al. Estimation of the epidemiological burden of human papillomavirus-related cancers and non-malignant diseases in men in Europe: a review. *BMC Cancer*; 12.
5. Falcaro M, Castanon A, Ndlela B, et al. The effects of the national HPV vaccination programme in England, UK, on cervical cancer and grade 3 cervical intraepithelial neoplasia incidence: A register-based observational study. *The Lancet* 2021; 398: 2084–2092.
6. Hintze JM, O’Neill JP. Strengthening the case for gender-neutral and the nonavalent HPV vaccine. *Eur Arch Otorhinolaryngol* 2018; 275: 857–65.
7. European Commission. *Europe’s beating cancer plan*. Brussels: European Commission, https://ec.europa.eu/health/system/files/2022-02/eu_cancer-plan_en_0.pdf (2021).
8. Brisson M, Bénard É, Drolet M, et al. Population-level impact, herd immunity, and elimination after human papillomavirus vaccination: A systematic review and meta-analysis of predictions from transmission-dynamic models. *Lancet Public Health* 2016; 1: e8–e17.
9. Bruni L, Saura-Lazaro A, Montoliu A, et al. HPV vaccination introduction worldwide and WHO and UNICEF estimates of national HPV immunization coverage 2010-2019. *Prev Med* 2021; 144: 106399.
10. Karafillakis E, Simas C, Jarrett C, et al. HPV vaccination in a context of public mistrust and uncertainty: A systematic literature review of determinants of HPV vaccine hesitancy in Europe. *Hum Vaccines Immunother* 2019; 15: 1615–1627.
11. Centre for Mental Health. *The economic and social costs of mental health problems in 2009/10*. London: Centre for Mental Health, 2010.
12. Aromataris E, Fernandez R, Godfrey C, et al. Chapter 10: Umbrella Reviews. In: Aromataris E, Munn Z (Editors). *JBI Manual for Evidence Synthesis*, <https://synthesismanual.jbi.global> (2020, accessed 31 July 2020).
13. Edwards D, Kelly D, Bennett C, et al. *An umbrella review of interventions used to improve HPV vaccine uptake in children, adolescents and young adults*. PROSPERO 2021 CRD42021273894 Available from:

- https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021273894. York: International Prospective Register of Systematic Reviews, https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=273894 (2021).
14. Campbell M, McKenzie JE, Sowden A, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. *BMJ* 2020; 368: l6890.
 15. McKenzie JE, Brennan SE. Chapter 12: Synthesizing and presenting findings using other methods. In: *In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021)*. Cochrane, www.training.cochrane.org/handbook. (2021).
 16. Thomas J, O'Mara-Eves A, Harden A, et al. Chapter 8: Synthesis methods for combining and configuring textual or mixed methods data. In: *An introduction to systematic reviews*. London: Sage Publications Limited, 2017, pp. 181–209.
 17. Ryan G, Avdic L, Daly E, et al. Influences on HPV vaccination across levels of the social ecological model: Perspectives from state level stakeholders. *Hum Vaccines Immunother* 2021; 17: 1006–1013.
 18. Kolff C, Scott V, Stockwell M. The use of technology to promote vaccination: A social ecological model based framework. *Hum Vaccines Immunother* 2018; 14: 1636–46.
 19. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; 372: n71.
 20. Abdullahi LH, Kagina BM, Ndze VN, et al. Improving vaccination uptake among adolescents. *Cochrane Database Syst Rev* 2020; 1: CD011895.
 21. Barnard M, Cole AC, Ward L, et al. Interventions to increase uptake of the human papillomavirus vaccine in unvaccinated college students: A systematic literature review. *Prev Med Rep* 2019; 14: 100884.
 22. Eisenhauer L, Hansen BR, Pandian V. Strategies to improve human papillomavirus vaccination rates among adolescents in family practice settings in the United States: A systematic review. *J Clin Nurs* 2021; 30: 341–56.
 23. Flood T, Wilson IM, Prue G, et al. Impact of school-based educational interventions in middle adolescent populations (15-17yrs) on human papillomavirus (HPV) vaccination uptake and perceptions/knowledge of HPV and its associated cancers: A systematic review. *Prev Med* 2020; 139: 106168.
 24. Fu LY, Bonhomme LA, Cooper SC, et al. Educational interventions to increase HPV vaccination acceptance: A systematic review. *Vaccine* 2014; 32: 1901–20.
 25. Ilozumba O, Schmidt P, Ket JCF, et al. Can mHealth interventions contribute to increased HPV vaccination uptake? A systematic review. *Prev Med Rep* 2021; 21: 101289.