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Knowledge and acceptance of Human Papillomavirus (HPV) and HPV vaccination in adolescent boys worldwide: a systematic review.

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HIGHLIGHTS

- Globally adolescent males have poor knowledge of HPV and HPV vaccination.
- Adolescent male knowledge of HPV is lower than their female peers.
- High knowledge of HPV is not always predictive of HPV vaccine acceptance.
- Standardised measures of HPV knowledge/acceptance used longitudinally are needed.
- Imperative to identify methods of increasing male adolescent awareness of HPV.

ABSTRACT

Aim: To determine HPV and HPV vaccine awareness, knowledge and acceptance in male adolescents worldwide.

Methods: A mixed methods systematic review was conducted. In accordance with PRISMA guidelines, relevant literature was identified through an electronic database search using specified keywords from inception to September 2015. Non-interventional studies presented in English that assessed HPV knowledge and provided data on male adolescents were included. If available, data on HPV and HPV vaccine perceptions, attitudes and/or HPV vaccine acceptance were also extracted. All studies were critically appraised to provide an indication of methodological quality. Results were compiled using a convergent synthesis.

Results: 22 papers were included. The majority of studies were cross-sectional and conducted in the US and Europe. Across continents, regardless of a country's HPV vaccination programme status, boys' knowledge of HPV and/or HPV vaccination was generally low to moderate and significantly lower than female knowledge or awareness. There was a disagreement in the association of knowledge and vaccine acceptance, with higher knowledge not always being predictive of acceptance.

Conclusions: Comparison and synthesis of research concerning HPV knowledge and attitudes was made difficult due to the lack of universal definition of vaccine acceptance, and no universally accepted tool for its measurement or for the measurement of HPV knowledge. It is imperative that future research utilises consistent measures of HPV knowledge and attitudes to facilitate interpretation and comparison across studies internationally. Prospective longitudinal studies would be more informative providing data on factors that influenced the move from vaccine intention to uptake.

KEYWORDS

HPV; Human papillomavirus; Systematic review; adolescents; men's health; cancer; cancer prevention; vaccination

INTRODUCTION

Human papillomavirus (HPV) is the most common sexually transmitted infection worldwide [1]. HPV infection is well-recognised as the causative agent in all cervical cancers; with two types (16/18) underpinning 70% of cervical cancer cases worldwide [2]. HPV is also linked to genital, anal [3], and oropharyngeal cancer (OPC) [4]. Approximately 95% of anal cancers are caused by HPV; 65% of vaginal cancers; 50% of vulvar cancers, and 35% of penile cancers [5]. OPC shows a regional/socio-economic variation; in comparison to the high-income areas of North America, Northern and Western Europe, Australia and Japan with a prevalence range of 39-56%, the rest of the world appears to have a lower prevalence (13-38%) [6]. In the United States (US), it is predicted that the number of HPV-related OPCs diagnosed per year will soon surpass the annual number of cervical cancer cases [7]. Infection with low-risk HPV (6/11) are also implicated in the development of genital warts [8].

Despite the impact of HPV on both sexes, few countries have implemented a vaccination programme for both adolescent boys and girls. Australia was the first country to initiate government-funded universal HPV vaccination, and began including boys in a national school-based HPV vaccination program in February 2013 [9]. The US also recommends universal vaccination, with the Vaccines for Children (VFC) Program funding HPV vaccination for children aged 9–18 years who are uninsured or underinsured [10]. The UK national school-based programme provides coverage for girls only as is the case in most European countries [11], with the exception of Austria who, in 2014, were the first in Europe to commence a publicly funded universal programme [12]. Switzerland recommend vaccination for boys and men aged 11 – 26 [13]. Within country, HPV vaccination for boys is recommended in Saxony (Germany) and Emilia-Romagna/Sicily (Italy). In Canada, of the thirteen provinces and territories, only Prince Edward Island, Alberta and Nova Scotia include boys in their school-based programme [14-17], although the provinces of Manitoba and Quebec may soon follow suit [18-19].

There is substantial debate around the inclusion of males in HPV vaccination programmes [20-21]. Many countries do not include men, and focus on achieving a high coverage in females to promote herd protection, i.e. a reduction in the risk of infection in males due to reduced exposure as a result of female vaccination. There is some emerging evidence that female only vaccination programmes with high female vaccination rates resulted in a one third reduction in the number of boys with genital warts [22]. The incremental benefit of extending the vaccine to males is believed to be dependent on coverage in females. With a low uptake in girls, the benefit of vaccinating boys is easily demonstrated; but when more

than 70% of females are vaccinated, the gender neutral vaccine approach appears less effective [23].

However, a female only vaccination strategy leaves a number of men vulnerable to HPV infection, and unvaccinated males are not protected if they move outside of the herd (due to migration or travel) and have sex with an unvaccinated partner. Additionally, this approach will have minimal effect on men-who-have-sex-with-men (MSM). In the UK, the Joint Committee on Vaccination and Immunisation (JCVI), while recognising the merits of universal gender-neutral vaccination, has recently released a recommendation that MSM under age 45 who attend Genito-Urinary Medicine (GUM) or HIV clinics should be offered vaccination [24]. Similarly, British Columbia (Canada) offers HPV vaccination for free to girls and “at-risk” boys (such as boys who are homeless or gay). This approach may have limited efficacy in preventing HPV-related disease, as a significant number of MSM may already have had sexual intercourse before presentation at GUM/HIV clinics [25]. In addition, for the HPV vaccine to be most effective, it should be given at a younger age (9-15 years), before exposure to HPV through sexual contact and when immunogenicity is at its most effective [26]. It is likely that the most effective, practical and ethical solution is to offer HPV vaccination to both adolescent males and females. There is also mounting evidence that universal vaccination is cost effective [27] particularly when the costs associated with oropharyngeal cancer [28] and genital warts treatment [29] are considered. A wider socio-economic perspective further supports this evidence, with increased benefit to society characterised through improved productivity, increased earnings and enhanced tax revenue due to vaccine related reductions in mortality and morbidity [30].

As countries are increasingly recommending and funding HPV vaccination for males, it is imperative to better understand the knowledge, awareness and attitudes of adolescent boys to HPV and HPV vaccination, in order to ensure uptake is maximised and both boys and girls are protected against HPV-related cancers in the future. The aim of this review was to determine the level of HPV and HPV vaccine knowledge and vaccine acceptance in male adolescents worldwide.

METHODS

A mixed methods systematic review including both quantitative and qualitative data was conducted.

Search strategy

In accordance with PRISMA guidelines, relevant literature was identified through an electronic database search of Medline (1966 – December 2015), CINAHL (1982 – December 2015), PsychINFO (1872 – December 2015), PsychARTICLES, Web of Science. Keywords to identify research into HPV knowledge and attitudes were taken from a previous publication focussed on men-who-have-sex-with-men (MSM) [31], and combined with search terms for male adolescents. Keywords used therefore were: (Human Papillomavirus OR HPV) AND (accept* OR aware* OR attitude* OR barrier * OR belie* OR behav* OR benefit* OR comprehend* OR communicat* OR cognit* OR cue OR decision OR educat* OR experience OR intent* OR know* OR motivat* OR norm* OR percep* OR perceive* OR prefer* OR psycholog* OR psychosocial OR represent* OR risk* OR side effect* OR subject* OR understand* OR will*) AND (male OR boy OR son) AND (adolescent* OR child*). The reference list of each relevant study was searched for additional relevant papers.

Eligibility criteria

Non-interventional studies presented in English that assessed HPV knowledge and provided data on male adolescents i.e. have you heard of HPV? and/or have you heard of HPV vaccine? were included. If available, data on HPV and HPV vaccine perceptions, attitudes and/or HPV vaccine acceptance were also extracted. An adolescent was operationalised in accordance with the WHO definition, which defines adolescence as after childhood, but before adulthood with an age range of 9 – 19, although for this review, the upper age limit was extended to 20 years, as many European secondary schools have an upper age limit of 20 years old [32]. Studies solely investigating the prevalence of HPV, studies not specific to HPV vaccination (i.e. general vaccination attitudes), those focused on parent or health care provider opinion on vaccination of adolescent males, and those including an immunosuppressed children or a HIV population were excluded. Reviews, editorials, comments and conference presentations were also excluded.

Study selection

Following completion of the database searching, and removal of duplicates, titles were divided between 2 reviewers (GP and RM). Studies were selected based on the inclusion/exclusion criteria. Any titles that lead to uncertainty were retained for abstract screening. Abstract and full-text screening was conducted by one reviewer (GP), any ambiguity in terms of study selection and the rationale for inclusion of the final studies were discussed with the review team.

Study quality

As per Patel et al. [32], to provide an indication of the quality of the included studies, all quantitative papers were assessed using a checklist created using the Centre for Evidence-Based Medicine (CEBM) tool for appraising survey studies and the guidance provided by Pettigrew and Roberts [33]. The Critical Appraisal Skills Programme tool was used to appraise the qualitative studies [34]. These two tools have been used previously in a review of adolescent HPV knowledge in Europe [32]. Two reviewers (RM and GP) completed the checklists for each included study, a third reviewer OS appraised those studies where the quality/fulfilment of criteria could not be agreed between the two main reviewers.

Data synthesis

Results of this systematic mixed studies review were compiled using a convergent synthesis [35]. A convergent synthesis involves initially synthesising qualitative and quantitative separately, then integrating the qualitative and quantitative summaries.

RESULTS

As can be seen from Figure 1, 113 studies met the initial inclusion criteria. On full text review, 91 were excluded as they did not focus on HPV specifically ($n = 6$), did not include adolescents ($n = 71$), had no separate male adolescent data ($n = 7$) or did not assess knowledge of HPV or HPV vaccination ($n = 7$). Twenty-two relevant publications were included and are summarised in Table 1. As can be seen from Table 1, three studies consist of the same sample and methodology, but report on different analysis [37,38,41]; consequently 20 studies have resulted in 22 separate publications. All studies were cross-sectional, with the majority ($n = 17$) using a self-administered questionnaire to assess HPV knowledge. Two studies used mixed methods [40,52] and one was solely qualitative [43]. Sample sizes ranged from 20 [57] to 2500 [52]. Participants were largely recruited from schools ($n = 13$), but online recruitment ($n = 2$), health centres ($n = 1$), or community sources ($n = 4$), were also used. There was wide representation from across the globe, although most of the included studies were conducted in the US ($n = 5$), Western Europe ($n = 7$) or Australia ($n = 2$). Nevertheless, one study was conducted in Africa [57], one in Hungary [48], one in Romania [42] and three in Asia [52-54].

Study quality

The methodological quality of the reviewed studies was generally acceptable, with the majority of studies ($n = 17$) being considered to be of moderate to high quality (see Table 2 and 3). The majority of quantitative/mixed method studies achieved a satisfactory response rate (59-100%) ($n = 15$), with only Samkange-Zeeb [44] not attaining a satisfactory level, although many did not base their sample size on a pre-study consideration of

statistical power ($n = 14$). The method of recruitment used by a number of studies lead to difficulty in generalising findings, as a large number of the included studies used a convenience sample, and only a few studies recruited in a way whereby the study sample could be considered representative of the population ($n = 7$). All studies were cross-sectional which prevents any statements to be made regarding causality.

HPV knowledge

All 20 studies either assessed knowledge of HPV or knowledge of HPV vaccination.

Of the 19 quantitative studies, 18 assessed awareness and/or knowledge of HPV (all except [36]), with varying methods of measurement. Eleven studies assessed awareness by asking an initial question 'Have you heard/are you aware of HPV?' [37,38,40-42,44,46-49,50,51,56]; this was followed by combinations of various HPV knowledge questions, largely focussed on what diseases are caused by HPV (different cancers types/genital warts), mode of HPV transmission, who can be affected by HPV, and how to protect against HPV. The remaining 7 studies also assessed knowledge in a variety of ways, from asking a broad question on 'What is HPV'/'What do you know about HPV?' with multiple-choice response options [45,54], or 'Is genital/cervical cancer caused by HPV?' [39,52], or "Have you ever discussed HPV with friends?" [55] Qualitatively, Hilton et al. [43] assessed HPV knowledge via discussions on awareness of disease, and understanding of disease process and symptoms.

Sixteen studies assessed awareness and/or knowledge of HPV vaccination [36,37,39,40,42,44,46-50,52-56]. Similar to HPV knowledge, 11 studies assessed awareness initially with a question on 'Have you heard of/are you aware of the HPV vaccine?' [36,37,39,40,42,44,48,49,50,52,53]. Moss et al [37] was the sole study to ask directly if respondents were aware that boys could receive the HPV vaccine. In two of these studies, the initial awareness question was followed by various other vaccine knowledge questions such as 'Can you get HPV by getting the vaccine?', 'Will the vaccine protect against other STIs?', 'When should the vaccine be given?' [40,49]. The remaining five studies did not include an initial awareness question, but assessed vaccine knowledge in a variety of ways including indicating yes/no to the statement 'The vaccine won't work if you are sexually active' [54-56], and asking participants to indicate from a list of answers 'What diseases are protected by the vaccine?' [54].

Across continents, regardless of a country's HPV vaccination programme status, boys' knowledge of HPV and/or HPV vaccination was generally low to moderate (5 – 65% had heard of HPV; 1 – 45% had heard of HPV vaccination)(Figure 2), and significantly lower than

female knowledge or awareness where it was compared [36,42,44,47,48,49,56], or at a similar level to the level of knowledge of unvaccinated females [45, 56]. Low knowledge in boys was also demonstrated in the qualitative study, where boys showed little knowledge of HPV, believing that it only affected female [43]. This is with the exception of three studies where knowledge in both genders was so low that no gender difference was noted [42,50,57]. Contrary to this, in two studies male adolescent knowledge was high including a study of adolescent males in Thailand [54] and a recent study of MSM aged 16-20 years in Australia [55]. Interestingly, Songthap et al. [54] found that boys had high knowledge that was comparable to females, but that most boys disagreed that 'HPV infection in men was as important as in women' [54].

Only studies in the US were conducted at a time when vaccination was available in country for adolescent males (since 2009), but despite this, low to moderate knowledge was still recorded (Figure 2) [36,37-41]. For example, a high quality, nationally representative sample survey found that only 25% of boys aged 11 – 17 years old were aware of HPV and 26% were aware of an HPV vaccine. Of those that were aware of the HPV vaccine, only 38% were aware that a vaccine was available for boys (approximately 10% of the overall sample) [37]. However, in a secondary analysis that examined the older 15 – 17 year old subsample [41], the percentage of adolescents who reported knowledge of HPV (not HPV vaccination) increased significantly from 25% to 40% ($p = 0.0003$) [41] indicating that age may influence HPV knowledge. (The study focussed on sexual disinhibition, so these items were not asked of younger boys). Indeed in other studies with higher male knowledge, the sample included participants over the age of 19 [47,49] which may have elevated the level of the sample's knowledge. This increased knowledge was also reported in another high quality US study that found adolescents over the age of 15 were more likely to report HPV vaccine awareness [36], although this study did not examine HPV knowledge. Contrarily, an older age group did not explain the high level of knowledge recorded in a high quality study of 12 – 15 year old Thai students [54]

It is also possible that it may not be age, but sexual activity that influences adolescent knowledge. Sexual orientation seems to impact on level of knowledge, with adolescent MSM having higher knowledge [40,55] although both of these studies are limited by their methodological quality. In Australia, in a study of 200 adolescent (16-20 years) MSM, there was a high level of knowledge, despite male vaccination not being routinely offered at the time of data collection [55]. In a study of urban, low income adolescents in the USA, conducted after the introduction of universal HPV vaccination, a high proportion (77%) of the 42% of males who had heard of HPV were MSM, although it should also be noted that the

mean age of MSM was 18 years old compared to the mean age of the heterosexual adolescents of 16 years [40]. It is possible that those who are identifying as MSM are older and therefore more sexually active (which may increase awareness). In addition, MSM may also have more frequent exposure to STI messages, more health discussions with their physician, and more experience of taking control of their sexual health. This possible association between age and/or sexual activity was also seen in a US study of inner city Caribbean and African American adolescents [39]. This study reported high levels of HPV knowledge in 13 – 19 years old; however, this is confounded by half of the sample being 18 or 19 years old, and 70% reporting sexual activity (98.6% with the opposite sex) [39]. It is important to note that this study was assessed as low quality and that HPV vaccines were administered to boys whose parents reported positive interest in receiving this immunization, which was done during the same clinic visit [39] and this may have impacted on outcome. This also occurred in the Australian MSM study, whereby the participating adolescent males were involved in another HPV infection study that offered free HPV vaccination at the end of the study [55].

As all studies were cross-sectional, it was not possible to determine if time (i.e. allowing HPV vaccination programmes to become more established) impacts level of knowledge.

HPV vaccine attitudes and acceptance

Association of HPV vaccine acceptance and HPV knowledge

Thirteen studies examined HPV vaccine acceptance [36-39,40,42,46,48,49,51,52,54,55,57], which was expressed as the percentage of adolescent boys who would be willing to be vaccinated against HPV. In the US (where vaccination was available for adolescent boys) the range for willingness to be vaccination was 30 [38] – 65% [39], one study reported actual vaccine uptake of 11.5% [36]. In Europe the range was 40% [49] – 75% [51]; Asia 25% [54] – 30% [52]; Australia 86% (MSM sample) [55], in Africa 100% willingness was reported [57].

There was a general association between level of knowledge and vaccine acceptability, with higher knowledge being associated with greater acceptability [39,40,42,46,49,55], although this data was generated from studies rated low to medium quality. For example, in the UK, boys who were unsure whether to have the vaccine they were significantly less likely to have heard of HPV (44%) compared with boys who intended (63%) ($X^2(1) = 9.35$, $p = 0.002$) or did not intend (58%) to receive the HPV vaccine ($X^2(1) = 6.46$, $p = 0.01$) [46]. Similarly, in the US, knowledge was associated with willingness to be vaccinated, with 65% of the adolescent boys who knew about HPV (i.e. that HPV is associated with genital cancer) being significantly associated with interest in receiving HPV vaccination [39]. However, as

previously stated, this was rated a low quality study, as vaccination was offered at end of study and this may have recruited participants more accepting of vaccination.

Notably, some studies (of medium to high quality) did not find a positive association between HPV knowledge and willingness to be vaccinated. For example, in a high quality US study conducted on a representative sample of adolescent boys from a rural location, 40% knew about HPV vaccination, but only 1.4% had received the full three doses of vaccine [36]. It should be noted that the adolescents in this study were not asked specifically if they knew the vaccine was available for boys, so they might have been only aware of female vaccination. This was also demonstrated in another high quality US study conducted on a nationally representative sample, where only 10% of male adolescents were aware of the existence of an HPV vaccine for boys specifically, while 26% were aware of the HPV vaccine in general [37]. This study also does not support the hypothesis that acceptance and knowledge are positively correlated, as despite low knowledge of HPV (10% of sample), almost 30% were willing to be vaccinated [37]. Similarly, in another high quality study conducted in Hungary, despite low knowledge in both primary and secondary school boys (20% and 29% respectively knew what HPV was), 60% of boys would request the vaccine if it was free [48]. Likewise in Mali, in a small study conducted prior to the introduction of an HPV vaccination programme, 100% of a convenience sample of adolescents (n = 20) aged 12 – 17 years, said they would be willing to be vaccinated, despite very low knowledge in both males and females [57]. A similar pattern was seen in another high quality study in Sweden [51] where despite low knowledge, 74% of 15-16 year old boys indicated they would like to be vaccinated.

Attitudes and HPV vaccine acceptance

The majority of studies also examined factors associated with acceptance [37-41,43,48-52,54,55,57]. Reasons for non-acceptance of vaccination were based around current sexual inactivity [42,46,51], regular condom use [39], or regular physical health examinations [39] and so the perceived risk of acquiring HPV was low. Those boys who had a high perceived likelihood of becoming infected [37], either from having a high number of sexual partners [39], previous STIs [39], or partaking in risky sexual behaviour [40] had a higher acceptance of vaccination. In addition, in a Swedish study, knowledge that the vaccine also protected against genital warts increased acceptance [51], which may indicate that the participants were more concerned or perceived themselves at greater risk of contracting genital warts.

Other reasons for vaccine acceptance were focused on severity, i.e. the perception that contracting HPV would have serious implications (largely around the fear of disease and risk

of developing cancer) [40,46,50,52], or regret if they later became infected with HPV [37], and wanting to protect future partners [37]. As noted earlier, it is important to differentiate between willingness to be vaccinated and actual receipt of vaccination, for example, and intention to receive the vaccine. In Sweden, 74% of boys aged 15 – 20 years indicated they would like to be vaccinated, but crucially only 4% had the intention of getting vaccinated in the future [50].

In addition to perceived low risk, other reasons boys expressed for not wanting to receive an HPV vaccine were regarding cost (price was too high) [48,55,57], and generic vaccination concerns such as worries about side effects [37,40,48,52], vaccine safety [54], fear of needles [43,48], or pain [37,42,43]. In India, low vaccine acceptance was also linked to recent media coverage of vaccine-related deaths [52].

DISCUSSION

In recent years, there has been an increase in studies examining knowledge and awareness of HPV in adolescent boys. This is likely reflective of changes in policies in an increasing number of countries worldwide to recommend a gender-neutral vaccine strategy. The majority of studies have been cross-sectional and conducted in the US and Europe; however, a small number of Asian and African countries have also examined the issue. This reflects a fundamental gap in knowledge and research on HPV and its implications given that low middle income countries (LMICs) report much higher prevalence of HPV (e.g. 33% in sub-Saharan Africa) [58], with all viral infections (including infection with HPV) leading to one fifth of cancer deaths in LMICs [59]. In addition, LMICs bear most of the burden of the global HIV epidemic [60]. The higher level of co-infection with HPV in those positive for HIV in the African population for example, increases associated cancer risk.

As can be noted from this systematic review, comparison and synthesis of research concerning HPV knowledge and attitudes is made more difficult to interpret as there is currently no universal definition of vaccine acceptance, and no universally accepted tool for its measurement or for the measurement of HPV knowledge. The included studies assessed knowledge differently, posing different questions to participants, for example, 'Have you ever heard of HPV?' or 'Which virus causes cervical cancer?'. However, regardless of question asked, it is important to note that adolescent male knowledge was statistically lower than their female counterparts. There appears to be a tiered level of knowledge and it is important to be able to distinguish between being aware of HPV; being aware that there are HPV vaccines; and knowing the vaccines are available for boys, which was highlighted in the nationally represented study of US adolescents [37]. This inconsistency between studies

makes comparison problematic, as the outcome of interest is measured in various ways, making it difficult to draw conclusions and recommendations and to develop methods to enhance vaccine acceptance.

In general, adolescent boys' knowledge of HPV was below that of female adolescents though there were exceptions to this, with two studies suggesting that female and male adolescent knowledge was so low no gender difference was detected [50,57], and a study of male adolescents in Thailand whose knowledge was as high as that of the female adolescents [54]. It was difficult in certain studies to separate the adolescent outcome from the young adult [39,44,47,49,52,55] and it is possible that the age of the sample and sexual experience could be contributing to the variability in knowledge reported. There is an indication that knowledge may increase with increasing age and sexual experience. We know that the HPV vaccine is most effective if given before commencement of sexual activity and hence possible exposure to HPV [61], therefore efforts to enhance knowledge and awareness need to be concentrated on younger adolescents.

Insufficient knowledge of HPV in adolescent boys may be reflective of many countries' information campaigns being targeted to females only, with a clear focus on cervical cancer. This connotation that HPV is a women's problem, and its subsequent impact on primary prevention efforts is referred to as the 'feminisation of HPV' [62]. This 'feminisation' is important as it impacts on how the general public, health care professionals and policy makers view HPV and HPV vaccination as a female only issue [62]. It is also possible that low male knowledge (compared to females) is due to males not being recommended or offered the HPV vaccine at time of data collection. This was not the case in the US; despite the vaccine being available for males at time of data collection; knowledge in adolescent males was still low. This could be reflective of how the vaccine is offered in the US via a health care practitioner and not offered through school-based programmes. This approach is leading to low vaccine uptake in the US, there is evidence to suggest that vaccine uptake in adolescent males is low; in 2012 only 20.8% of US boys aged 13 – 17 received at least one dose, and only 6.8% receiving the full three dose schedule [63]. This can be contrasted with a school-based universal vaccination programme in the Canadian province of Prince Edward Island, where 79% of adolescent boys received all three doses of vaccination (although again male vaccination was significantly lower than females (85%; $p=0.004$)) [64]. Based on the prevailing evidence, what is needed is better health education and public information to maximise public awareness that HPV affects both men and women and should be of concern of both sexes. As illustrated by Hoglund et al. [50], it is possible that HPV vaccine marketing has only reached health care professionals and not the general

public and this may be why adolescent HPV knowledge is so low. Nevertheless, it is crucial that when HPV is marketed to the general public it is not presented as a vaccine for females, but as a universal vaccine for all [62].

Although knowledge is low, it is important to note that knowledge was not always predictive of vaccine acceptance and uptake. In this review, the high quality studies indicated that knowledge was not predictive of willingness to be vaccinated or actual vaccine uptake. Parental and health care provider knowledge, acceptance and recommendation, though not specifically examined in this review, was seen as an important correlate of vaccine acceptance in adolescents [36,40,43]. There is an opportunity for education to extend beyond vaccination to HPV transmission and other prevention measures. As knowledge and acceptance are not always correlated, i.e. an adolescent may consider vaccination without adequate knowledge, health care professionals responsible for vaccination should use the opportunity to inform adolescents about HPV and its associated cancers. In research studies, we should not look at knowledge in isolation as it is not always predictive of uptake; in research of this nature; attitudes to vaccination may be more informative. Although there may be a discrepancy between vaccine intent and actual receipt of vaccination. The cross-sectional nature of the research included in this review makes it difficult to determine if vaccine acceptance or intent to vaccinate leads to actual vaccine uptake.

Few studies on vaccine acceptance in adolescent boys are guided by a theoretical framework around decision making or behaviour change, which makes the identification and exploration of factors that influence vaccine uptake difficult. In future research, a theoretical framework such as the Precaution Adoption Process Model (PAPM), a model of behaviour change with six stages of decision-making [65], may be beneficial for work of this nature. The PAPM categorises individuals as 1) unaware 2) unengaged, 3) undecided 4) decided not to act 5) decided to act 6) acting. This model applied in a longitudinal survey would allow for the crucial identification of factors that caused the change in health behaviour. The PAPM is suited to research in vaccine acceptance and uptake, as it identifies those who are aware of the vaccine but decided not to act. The categorisation of individuals who have decided to act and those individuals who have acted (i.e. received the vaccine) allows the crucial identification of factors that lead individuals to receive the vaccine. It is likely that a different intervention would be needed for individuals at different stages of the PAPM. For example, someone is stage 1 (unaware) may benefit most from awareness raising interventions in the media or from health care professionals; whereas someone who has decided to act may need assistance in accessing the vaccine.

Future research recommendations

It is imperative that future research utilises consistent measures of HPV knowledge and attitudes to facilitate interpretation and comparison across studies internationally. One scale that could be used is that developed by Waller et al [66], which has demonstrated satisfactory psychometric properties and could be appropriately adapted for use to various other populations, for example, adolescents. Prospective longitudinal studies designed and informed by the PAPM as described above, would be more informative providing data on factors that influenced the move from vaccine intention to uptake. In addition, more complex research designs to determine whether age or sexual activity impact on HPV and HPV vaccine knowledge would be beneficial.

From a policy perspective, it is important to identify ways in which awareness among male adolescents can be increased, while also using an evidence based approach to support recommendations regarding universal HPV vaccination. More in depth analysis of the reasons for high awareness among male adolescents in countries such as Thailand may provide valuable insights that can have broader application. Data from countries/regions where HPV vaccination in males has been implemented can help inform policy decision making, and this data should include health economic analysis concerning the cost effectiveness of a universal vaccination approach. Public awareness campaigns such as HPV Action's "Jabs for the Boys" in the UK can also be effective, particularly if they are linked with effective lobbying of decision makers by coalitions of healthcare professionals and patient advocates

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Figure 1 PRISMA flow diagram

Figure 2 HPV and HPV vaccine knowledge grouped per Continent

Table 1: Included studies table

Study	Design	Country and vaccine status**	Sample	HPV vaccine status	Setting	HPV knowledge/HPV vaccine knowledge	HPV acceptance (% boys vaccinated/willing to be vaccinated)	Factors associated with acceptance.	Study quality
Americas									
Bhatta 2015 [36]	C/S YRBSS	USA; boys aged 9-26	1299 (674 boys, 625 girls) 11 – 18 years Rural Appalachian Ohio RR 69-82%	11.5% boys have received 1 dose hpv vaccine	School	Assessed knowledge of HPV vaccine only. 42.1% boys knew about HPV vaccine.	11.5% boys have received 1 dose of HPV vaccine. 1.4% received all 3 doses.	Not examined	H
**Moss 2015 [37] And Reiter 2011 [38]	C/S Online SAQ	USA;	412 boys 11 – 17 years National sample; 2010 HIS study RR 73%	NK	Online	Assessed knowledge of HPV and knowledge of HPV vaccine. 25% aware of HPV, 26% aware of vaccine, of these 38% aware that boys can receive vaccine.	28.9% were willing to be vaccinated.	3.57 believed it was important to protect health (on 5 point scale). Perceived likelihood of getting HPV was 2.02 (on 4 point scale). Anticipated regret of HPV infection was 3.14 (on 4 point scale).	H
Shao 2015 [39]	C/S SAQ 2011 - 2012	USA; boys 9 -26	101 Caribbean and AA boys range 13 - 19; 53 (13-17); 48 (18+). RR 79%	NK	Medical clinic	Assessed knowledge of HPV and knowledge of HPV vaccine. 65% knew what HPV was; 27% knew HPV caused cervical cancer and rectal cancer in males. 45% heard of the vaccine.	65% interested in receiving the vaccine Higher knowledge associated with greater acceptability.	Condom use reduced interest in HPV vaccine; increase no of sexual partners increased interest in vaccine. Routine physical exam less likely to have an interest in vaccine; previous STI increased interest.	L

Gutierrez 2013 [40]	C/S SAQ and FG	USA; boys aged 9-26	76 boys 13 – 21 years Urban; Low income; Philadelphia RR ?	UV	Comm	Assessed knowledge of HPV and knowledge of HPV vaccine. 42% heard of HPV (77% MSM), 39% heard of vaccine [18% heterosexual heard of HPV; 77% MSM]	50% said they would get vaccinated within the next 12 months. Higher knowledge associated with greater acceptability.	60% boys believe vaccination would be easy. 68% believe getting vaccinated is smart. 64% believe vaccination is safe.	L
Mayer 2013 [41]	C/S Online SAQ	USA; boys 9-26	176 boys 15 – 17 years National sample. RR 73%	V and UV	online	Assessed knowledge of HPV only. 40% heard of HPV; 15% heard of HPV, with low knowledge. 25% heard of HPV, high knowledge.	Percentage willingness not assessed, although perceived likelihood of getting HPV was 2.09 on a 4 point scale (1=no chance, 4=high chance)	Perceived peer acceptance of vaccine was 3.06 on 5 point scale (1=strongly disagree, 5=strongly agree), Anticipated regret if didn't get HPV vaccine and later got HPV infection was 3.16 on 4 point scale (1= nothing at all, 5= a lot)	H
<i>** Reiter et al., 2011; Moss et al., 2015 and Mayer et al., 2013 all report on data from the 2010 HPV Immunization in Sons (HIS) Study. Mayer used a subsample of boys aged 15 – 17 years as their study focussed on sexual disinhibition, these items were not asked of younger sons.</i>									
EUROPE									
Maier 2015 [42]	C/S SAQ	Romania; no male vaccine	524 (262 boys, 262 girls) 16 – 18 years Two schools in Bucharest	UV	School	Assessed knowledge of HPV and knowledge of HPV vaccine. 17% boys heard of HPV; 8% boys heard of the vaccine. Significantly lower than girls. No significant difference in knowledge scores between boys and girls. Only 6.6% had high knowledge, 60% fair knowledge, 34% low knowledge.	If they received more information on vaccination, 43% of boys would be willing to be vaccinated.	Lack of information	M

Hilton 2013 [43]	C/S FG	Scotland; no male vaccine	59 (30 boys, 29 girls) 13 – 18 years Diverse sample	UV	Comm	Assessed HPV knowledge via discussions on awareness of disease, and understanding of disease process and symptoms Boys demonstrated little awareness of HPV, believed it affected only females	Not examined.	Viewed as a prevalent infection and a serious disease. Fear of needles and pain.	
Samkang e-Zeeb 2013 [44]	C/S SAQ 2011	Germany ; no male vaccine	1148 (632 females and 516 Males) 12-20 years old Bremen and Bremerhaven Northern Germany RR 28%	UV	School	Assessed knowledge of HPV and knowledge of HPV vaccine. Significantly more females than males had heard of HPV (18 vs. 8 %) 15% of boys aware that HPV causes cervical cancer; 9% of boys aware of HPV vaccination.	Not examined	Not examined	M
Stocker 2013 [45]	C/S SAQ 2010	Germany; no male vaccine	442 (238 girls, 204 boys) 13 – 19 years Berlin RR 59%	60% girls V	School	Assessed knowledge of HPV only. Boys showed same trend in knowledge as unvaccinated girls. Boys had less knowledge than vaccinated girls, but only slightly less than unvaccinated girls. 43.9% knew HPV caused cervical cancer and penile cancer	Not assessed in boys	Not assessed in boys	M
Forster 2012 [46]	C/S SAQ	England; no male vaccine	528 boys 16 – 18 years One school SE	UV	School	Assessed knowledge of HPV and knowledge of HPV vaccine.	41% willing to receive vaccine. Boys who were unsure	To protect health. Current sexual inactivity.	M

			England RR 89%			52% boys aware of HPV	whether to have the vaccine were significantly less likely to have heard of HPV (44%) compared with boys who intended (63%) or did not intend (58%) to have it.		
Sopracor devole 2012 [47]	C/S SAQ 2009	Italy; no male vaccine Third year of female vaccine	1105 (476 males, 629 females) 13 – 23 years (mean 15) One town NE Italy RR 100%	45.4% girls vaccinated	School	Assessed knowledge of HPV and knowledge of HPV vaccine. 51.3% boys heard of HPV (92.8% girls) better knowledge reported by girls. Of those who were aware of HPV, more girls knew about the vaccine (94.5% v 71.3%)	Not examined	Not examined	M
Marek 2011 [48]	C/S SAQ	Hungary; no male vaccine	1769 (820 boys, 949 girls) 12 – 19 years National sample RR 90%	UV	School	Assessed knowledge of HPV and knowledge of HPV vaccine. 20% primary school boys and 29% secondary school boys heard of HPV. Of those who had heard of HPV; 45% primary and 47% secondary boys know HPV linked to CC. 27% and 34% aware of link to genital warts.	60% of boys would accept the vaccine if it was free.	86% believed in the effectiveness of the vaccine. 60% primary and 61% secondary boys would request vaccine if it was free. 40% and 35% would pay for vaccine. Worries around side effects.	H
Pelucchi 2010 [49]	C/S SAQ 2008	Italy; no male vaccine First year of female vaccine	M = 209; F = 649 14 – 20 years Milan, northern Italy	UV	School	Assessed knowledge of HPV and knowledge of HPV vaccine. Males had less knowledge of HPV (72 v 51%), thought it concerned them (only	68% girls v 40% males said they would undergo vaccination.	The students who were aware that HPV could affect them (felt at risk) were more in favour of vaccination regardless of whether or not they were M or F	M

			RR 79%			26% boys thought it did concern them versus 45% girls), the purpose of HPV vac (75 v 63% of those who had heard of HPV)			
Hoglund 2009 [50]	C/S SAQ	Sweden; no male vaccine	459 (209 boys, 250 girls) 15 – 20 years One town RR 80%	UV	School	Assessed knowledge of HPV and knowledge of HPV vaccine. 5% of total participants had heard of HPV, 1% aware of vaccine, 2% aware that boys can contract HPV. No difference between boys and girls.	Not examined	Not examined	M
Gottvall 2009 [51]	C/S SAQ	Sweden; no male vaccine	608 (347 girls, 261 boys) 15 – 16 years RR 86%	UV	School	Assessed knowledge of HPV only Virus 9.6% (boys only)	74.3% boys would like vaccine High acceptance despite low knowledge	76.3% believe vaccine is effective Current sexual inactivity Knowledge that vaccine protected against GW increased acceptance	H
ASIA									
Hussain 2014 [52]	C/S SAQ and SSI	India; no male vaccine	2500 (1570 girls, 930 boys) 1033 12-18 years Urban and rural RR 96%	UV	School/ University	Assessed knowledge of HPV and knowledge of HPV vaccine. Very low level of knowledge – 15% of total sample aware of cervical cancer. Of 930 males, 103 knew HPV caused cancer (11%), and 63 knew of the vaccine (7%). Female knowledge significantly higher.	29.7% boys would be willing to have vaccine	"a negative response was documented with respect to implementation of vaccination programme in India due to adverse effects of vaccine related deaths recently"	L

Tang 2014 [53]	C/S SAQ	China; no male vaccine	848 (452 girls, 396 boys) 14-18 years RR 94%	UV	School	Assessed knowledge of HPV and knowledge of HPV vaccine. Virus 10%, vaccine 9.1% Gender difference in knowledge scores	Not examined	Not examined	H
Songthap 2012 [54]	C/S SAQ	Thailand; no male vaccine	644 (343 girls, 301 boys). 12-15 years Bangkok RR 80%	UV	School	Assessed knowledge of HPV and knowledge of HPV vaccine. Vaccine 60.18% (boys only) 80% boys had knowledge of HPV. No gender difference in scores.	Willingness to get vaccine 25.3% in favour, 52.4% unsure, 22.3% against	Availability, education, efficacy 37.2%	H
OCEANIA									
Zou 2014 [55]	C/S SAQ 2010 - 2012	Australia; female only at time of study [male vaccine 2013]	200 MSM 16 – 20 years Melbourne RR?	UV	Comm and other	Assessed knowledge of HPV and knowledge of HPV vaccine. High level of HPV knowledge	High acceptance - If vaccine free, 86% willing to disclose their sexuality to receive the vaccine	80% not willing to purchase the vaccine because of its cost.	M
Agius 2010 [56]	C/S SAQ 2008	Australia; Female vaccine at time of data collection	1927 (793 boys, 1134 girls) 14-20 years Nationally representative RR 66%	UV	School	Assessed knowledge of HPV and knowledge of HPV vaccine. 19.2% boys aware of virus 8.5% boys aware of vaccine availability	Not examined	Not examined	M

AFRICA									
Poole 2013 [57]	C/S SSI 2011	Mali; no male vaccine. Prior to HPV vaccine licensing	adolescents: 20 (12 male) 14 years Convenience sample RR 98%	UV	in own home	Assessed knowledge of HPV Low levels of knowledge in both genders.	100% said they'd be willing to receive the vaccine (despite low knowledge).	Vaccine price	M

C/S = cross-sectional; SAQ = self-administered questionnaire; YRBSS = The Youth Risk Behavior Surveillance System; V = vaccinated; UV = unvaccinated; RR = response rate; NK = not known; comm = community

Table 2: Critical Appraisal of quantitative/mixed methods studies

	Did the study address a clearly focused question /issue?	Is the research method appropriate for answering the research question?	Is the method of selection of the subjects clearly described?	Could the way the sample was obtained introduce selection bias?	Was the sample of subjects representative with regard to the population to which the findings will be referred?	Was the sample size based on pre-study considerations of statistical power?	Was a satisfactory response rate achieved?	Are the measurements (questionnaires) likely to be valid and reliable?	Was the statistical significance assessed?	Could there be confounding factors that haven't been accounted for?	Overall study quality
US											
Bhatta 2015	Y	Y	Y	N	Y	N	Y	Y	Y	N	H
Moss 2015/Mayer 2013/Reiter 2011	Y	Y	Y	N	Y	N	Y	Y	Y	N	H
Shao 2015	Y	Y	N	Y	N	N	Y	CT	Y	N	L
Gutierrez 2013	Y	Y	N	Y	N	N	CT	CT	Y	N	L
EUROPE											
Maier 2015	Y	Y	Y	Y	N	N	CT	Y	Y	N	M
Stocker 2013	Y	Y	Y	Y	N	Y	Y	Y	Y	N	M
Samkange-Zeeb 2013	Y	Y	Y	N	Y	N	N	CT	Y	N	M
Forster 2012	Y	Y	Y	Y	N	N	Y	CT	Y	N	M
Sopracordevole 2012	Y	Y	Y	Y	N	N	Y	Y	Y	N	M
Marek 2012	Y	Y	Y	N	Y	N	Y	Y	Y	N	H
Pelucchi 2010	Y	Y	Y	Y	N	N	Y	Y	Y	N	M
Hoglund 2009	Y	Y	Y	N	Y	N	Y	CT	Y	N	M
Gottvall 2009	Y	Y	Y	N	N	Y	Y	Y	Y	N	H
OCEANIA											
Zou 2014	Y	Y	Y	Y	N	Y	CT	CT	Y	N	M
Agius 2010	Y	Y	Y	N	Y	N	Y	N	Y	N	M
AFRICA											

Poole 2013	Y	Y	Y	Y	N	N	Y	N	Y	N	M
ASIA											
Hussain 2014	Y	Y	N	CT	N	N	Y	CT	Y	N	L
Tang 2014	Y	Y	Y	N	Y	Y	Y	Y	Y	N	H
Songthap 2012	Y	Y	Y	N	N	Y	Y	Y	Y	N	H

Y = Yes N = No CT = Can't tell

Table 3: Critical appraisal of qualitative studies

	Clear aim?	Qualitative method appropriate?	Appropriate design?	Appropriate recruitment?	Data collection adequate?	Researcher relationship	Ethical issues	Data analysis	Clear statement of findings?	Valuable?
Hilton 2013	Y	Y	Y	Y Various recruitment sources, purposive sampling, diverse sample	No mention of data saturation, limited justification for focus groups	Not discussed	Not discussed	Y	Y	Limited generalisability. Gave suggestions for future research.

Y = Yes N = No CT = Can't tell