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Review

Efficacy of human papillomavirus vaccines in the prevention of male genital diseases: a systematic review

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Objectives

To evaluate the results of randomised controlled trials (RCTs) regarding the efficacy of human papillomavirus (HPV) vaccination in preventing male genital-related diseases.

Methods

A systematic search of English language literature using PubMed, Scopus, and Cochrane Library was performed in April 2024 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol.

Results

Evidence from four RCTs (including 7008 male participants) support the efficacy of the quadrivalent HPV vaccine in preventing genital warts and persistent HPV infection in HPV-naïve men. The low incidence of male genital malignancies in the control groups of the reported studies lead to underpowered evidence. However, vaccination leads to durable protection with a long-term follow-up of 10 years showing efficacy of 91.8% to prevent HPV 6-, 11-, 16-, or 18-related external genital lesions (EGLs) in HPV-naïve subjects. Additionally, the quadrivalent vaccine seems to effectively reduce the detection of DNA from all four HPV types.

Conclusion

In summary, early quadrivalent HPV vaccination demonstrates efficacy in preventing HPV infection and EGLs in males. Well controlled prospective studies are needed to confirm the long-term efficacy, specifically in cancer prevention, in all men and specific subject subgroups, and to identify the targeted population who is most likely to benefit from early vaccination.

Keywords

Genital cancers, genital disease, human papillomavirus (HPV), male, vaccine

Introduction

Genital human papillomavirus (HPV) infection has a high and widespread global prevalence in men, with approximately one-third of men worldwide infected with at least one genital HPV type and one-fifth infected with high-risk HPV types; indeed, the disease burden associated with HPV has been steadily increasing in the male population, particularly in high-income countries [1].

Human papillomavirus infections in men have been linked to various men's health issues, including 33% of penile cancers

attributed to high-risk HPV, benign genital warts, decreased male fertility, and the potential for asymptomatic genital infections to serve as sources of partner infection, underscoring the importance of primary and secondary prevention strategies for this disease [2,3]. However, HPV vaccination rates in men is limited in its uptake by factors such as local awareness and false concerns regarding its safety. HPV vaccine's efficacy in the primary and secondary prevention of male genital diseases has also been questioned; if data would be made available and communicated, it would help its uptake.

Human papillomavirus vaccination in males has been implemented in a handful of countries, including Australia, Canada, the USA, and Austria [3,4]. In this systematic review, we summarise the results of randomised controlled trials (RCTs) regarding the efficacy of HPV vaccination in preventing male genital-related diseases.

Methods

Search Strategy

We conducted this systematic review of RCTs assessing HPV vaccination efficacy for prevention of male genital diseases according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol [5]. A full electronic literature search using PubMed, Scopus, and Cochrane Library was performed by two independent authors in April 2024 to find relevant studies. After the primary screening based on study title and abstract, all full-text papers were assessed and excluded with reasons. Any discrepancies were resolved by referring to the senior author. The following terms were used in our search strategy: ((vaccination OR vaccine OR immunization OR Gardasil OR Cervarix) AND (HPV OR human papilloma virus OR human papillomavirus)) AND (randomized controlled trial OR RCT OR prospective study). The protocol of this systematic review was registered in the International Prospective Register of Systematic Reviews database (PROSPERO, CRD42024530546).

Inclusion Criteria

We used the Population, Intervention, Comparator, Outcome, and Study (PICOS) design to assess the eligibility criteria. The studies were considered eligible if male participants (population) who had undergone HPV vaccination (intervention) were compared to male participants who had received placebo (comparator) to determine the differential effects of HPV vaccination on outcomes of interest (outcome) in randomised studies only (study design). HPV-related external genital lesions (EGLs) rate was considered as primary outcome and persistent genital HPV infection rate was defined as secondary outcome of interest. We excluded conference abstracts, replies, editorial comments, review articles, and written in non-English language.

Data Extraction

Two investigators independently extracted data on first author, year of publication, region of study, recruitment period, HPV vaccine type, HPV vaccination protocol, efficacy objective, measures of efficacy, study population characteristics, number of subjects, participants' age, efficacy of vaccine, and follow-up duration.

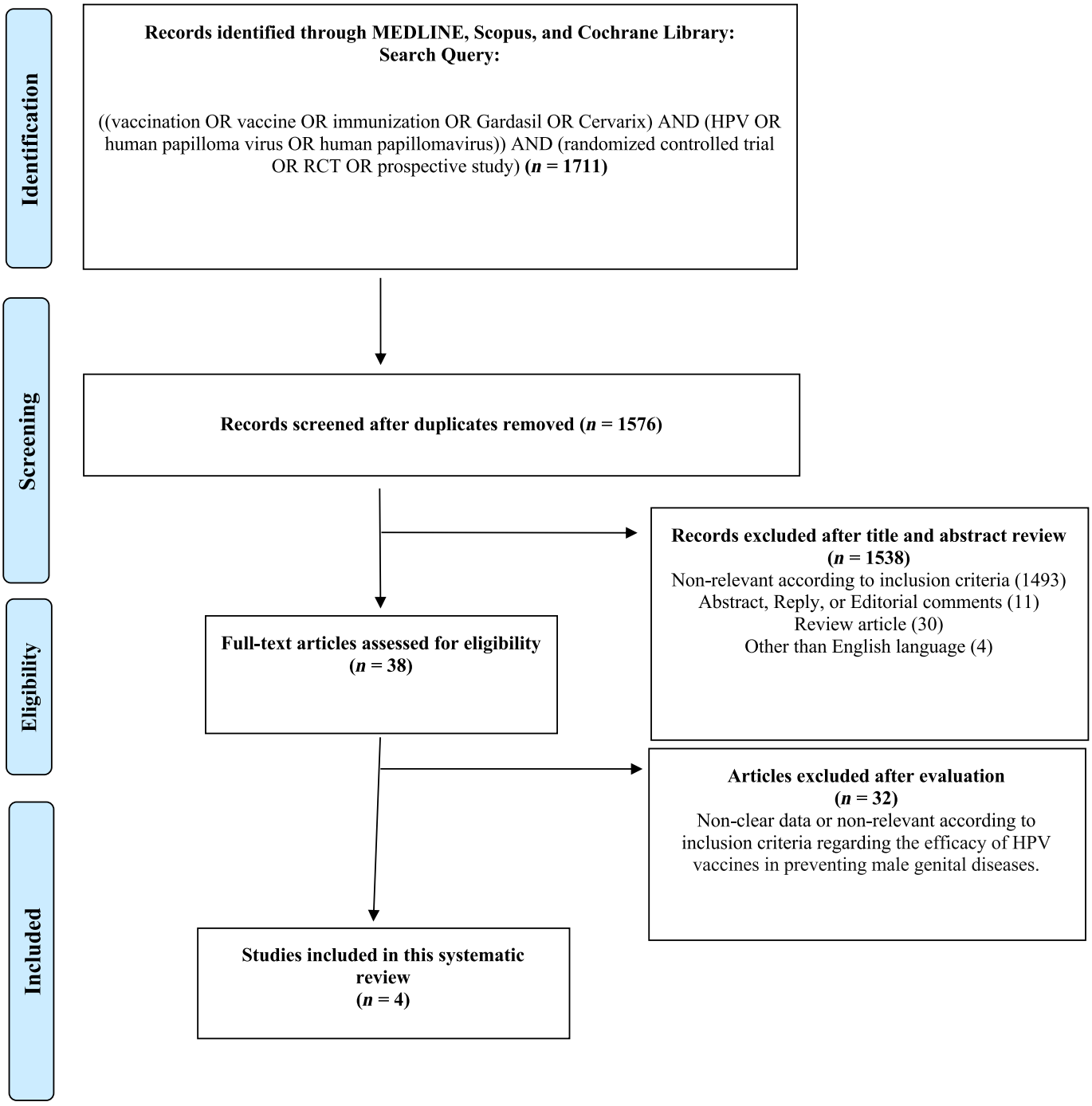
Results

A total of 1711 studies were identified by our initial literature search and 135 duplicates were removed. Then, 1538 and 32 articles were excluded after title/abstract evaluation and full-text assessment, respectively. Finally, four RCTs were included for qualitative evidence synthesis, (Fig. 1). The characteristics of the RCTs and the clinical data are described in Tables 1 and 2 [6,7,9,10]. These studies were published between 2011 and 2022 and included 7008 male participants.

Human Papillomavirus Vaccination and EGLs

Results from two RCTs support the efficacy of the quadrivalent HPV vaccine for primary prevention of HPV-related EGLs, including external genital warts, penile intraepithelial neoplasia (PIN) and perineal intraepithelial neoplasia, and penile, as well as perineal cancers in males [6,7]. Giuliano et al. [7] reported an observed efficacy of 90.4% (95% CI 69.2–98.1%) for quadrivalent HPV vaccine against type 6-, 11-, 16-, or 18-related EGLs in the per protocol population (PPP), which consisted of males who were seronegative on Day 1, PCR-negative for both swab and biopsy specimens, and who received all three vaccinations within 1 year. However, in the intention-to-treat population (ITP) the efficacy was limited to 65.5% (95% CI 45.8–78.6%). This is supposedly because some males may have not received all the doses of vaccine, might have been already seropositive at enrolment, or might have had positive results for the quadrivalent HPV vaccine types on PCR assay. While vaccination was effective in reducing the development of condylomata acuminata in the PPP and ITP, there was no significant difference in efficacy observed between the vaccine and placebo groups in terms of the development of PIN, as well as penile and perineal cancer. However, the low incidence of HPV-related pre-malignant and malignant EGLs limits any conclusions with regard to these endpoints, specifically as the trials were not powered to assess these endpoints [8]. Indeed, only 15% of included subjects were men who have sex with men in the four RCTs [6,7,9,10], despite this particular population bearing a disproportionately higher burden of HPV infections and related diseases,

Fig. 1 The PRISMA flow chart for article selection process to summarise the efficacy of HPV vaccines in preventing male genital diseases.



including cancers. This leads to a low incidence of cancer-related events limiting definitive conclusions on cancer-related endpoints in males, in contrast to women [11].

Given the lifelong risk of HPV infection in men, Goldstone et al. [6] conducted a long-term follow-up extension study to assess the durability of quadrivalent HPV vaccine protection. They demonstrated an efficacy of 91.8% (95% CI 69.4–98.6%) for HPV 6, 11, 16, or 18-related EGLs in the PPP. This efficacy was observed when comparing the early vaccination group, who received one or more doses of the quadrivalent HPV vaccine in the base study with a median follow-up of 10 years, to placebo recipients who were offered the

Table 1 Study characteristics of four RCTs assessing the clinical efficacy of HPV vaccination for prevention of male genital diseases.

Reference	Region	Recruitment period	HPV vaccine type	HPV vaccination protocol	Efficacy objective	Measures of efficacy	Study population for analysis	
							ITT	PPP
Giuliano et al., 2011 [7]	Africa, Asia-Pacific, Europe, Latin America, North America	2004–2008	Quadrivalent HPV L1 vaccine (HPV 6, 11, 16, and 18)	Three doses: Day 1, Month 2, and Month 6	EGL related to HPV 6, 11, 16, or 18* Reduction the incidence of persistent HPV infection EGL related to any HPV type	Genital examinations on Day 1 and at Month 7, 12, 18, 24, 30 and 36 Biopsies of EGL HPV testing and PCR assay of nail file and Dacron swab specimen of EGL on Day 1 and at Month 7, 12, 18, 24, 30, and 36	Received one or more doses of vaccine or placebo and returned for follow-up Might have been seropositive at enrolment Might have had positive results for the quadrivalent HPV vaccine types on PCR assay	Seronegative on Day 1 and PCR-negative for both swab and biopsy specimens from Day 1 through Month 7 for the relevant vaccine HPV type No protocol violations Received all three vaccinations within 1 year and had one or more follow-up visits after Month 7
Coskuner et al., 2014 [10]	Europe	2009–2013	Quadrivalent HPV L1 vaccine (HPV 6, 11, 16, and 18)	Three doses: Day 1, Month 2, and Month 6	Reduction the incidence of genital wart	Genital examinations: genital warts were visibly diagnosed with magnifying glass after aceto-white test application whenever deemed necessary Pathological examination in suspicious cases	Men with genital warts after the initial treatment intervention (local excision with electrocautery in larger pedunculated lesions or electrocautery alone in flat broad-based lesions)	_
Mikamo et al., 2019 [9]	Asia	2013–2017	Quadrivalent HPV L1 vaccine (HPV 6, 11, 16, and 18)	Three doses: Day 1, Month 2, and Month 6	HPV 6-, 11-, 16-, 18-related persistent anogenital infection (detected at ≥2 consecutive visits ≥6 months apart)	Genital examinations on Day 1 and at Month 7 and 12, and every 6 months thereafter Biopsies of EGL HPV testing and PCR assay of nail file and Dacron swab specimen of EGL	_	Received all three vaccinations Seronegative at Day 1 and PCR negative from Day 1 to Month 7 to the relevant HPV type
Goldstone et al., 2022 [6]	Africa, Asia-Pacific, Europe, Latin America, North America	2010–2017	Quadrivalent HPV L1 vaccine (HPV-6, 11, 16, and 18)	Three doses: Day 1, Month 2, and Month 6	EGL related to HPV 6, 11, 16, or 18* External genital warts related to HPV 6 and 11	Genital examinations on Day 1 and at Month 7, 12, 18, 24, 30, and 36† Biopsies of EGL HPV testing and PCR assay of nail file and Dacron swab specimen of EGL on Day 1 and at Month 7, 12, 18, 24, 30, and 36	Received at least one vaccine dose Seronegative and PCR-negative for HPV types analysed from Day 1 of the base study to the final follow-up visit before receiving the quadrivalent HPV vaccine Had at least one long-term follow-up visit	Received all three doses Seronegative at Day 1 and PCR-negative from Day 1 through Month 7 of the base study for the HPV type being analysed No protocol violations Had attended at least one visit during the long-term follow-up study

**External genital lesions related to HPV 6, 11, 16, or 18 including (condylomata acuminata [external genital warts]; PIN, perianal or perineal intraepithelial neoplasia; or penile or perineal cancer. †Detailed anogenital examinations were done yearly during long-term follow-up.*

three-dose quadrivalent HPV vaccine at the end of the base study ('catch-up' vaccination group). During the long-term follow-up period, there were no new cases of external genital warts related to HPV 6 or 11, nor EGLs related to HPV 6, 11, 16, or 18 in either the early vaccination or the 'catch-up' vaccination groups. However, a lower vaccination efficacy of 81.8% (95% CI 55.9–92.6%) for the ITP suggests that HPV-naïve subjects benefit more from vaccination in terms of developing HPV-related EGLs [6,7].

Human Papillomavirus Vaccination and Persistent Genital HPV Infection

Two RCTs reported efficacies of 85.6% (95% CI 73.4–92.9%) and 85.9% (95% CI 52.7–97.3%) of the quadrivalent HPV vaccine for Type 6-, 11-, 16-, or 18-related persistent infection in HPV-naïve male subjects [7,9]. The vaccine was also efficacious in reducing the detection of DNA for all four HPV types, with an efficacy of 44.7% (95% CI 31.5–55.6%). Indeed, significant reductions in DNA detection for individual HPV types ranged from 41.1% for HPV 16 (95% CI 18.5–57.7%) to 62.1% for HPV 18 (95% CI 39.2–77.1%) [7]. While the reported efficacy of the vaccine in reducing high-risk HPV DNA is not exceptionally high, this remains an important topic, especially considering the potential transmission of disease to a sexual partner due to persistence of the infection and shedding of HPV DNA [12].

Human Papillomavirus Vaccination and Secondary Prevention

Coskuner et al. [10] assessed the secondary prevention efficacy of the quadrivalent HPV vaccine in a RCT involving 171 men with genital warts following initial treatment intervention using electrocautery. With a mean follow-up of 46.1 months, vaccination was not associated with a decrease in the recurrence rate of genital warts in a multivariable analysis that adjusted for the effects of confounding factors. HPV vaccination seems thus to have a limited efficacy in preventing wart recurrence in non-HPV-naïve males who already had HPV-related warts.

Table 2 Patient characteristics in and vaccine efficacy results in four RCTs assessing the clinical efficacy of HPV vaccination for prevention of male genital diseases.

Reference	Number of subjects*	Age, years, mean*	Efficacy of quadrivalent vaccine vs placebo % (95% CI)			
			HPV type EGL		Condyloma acuminata	
			PPP	ITP	PPP	ITP
Giuliano et al., 2011 [7]	2032 vs 2033	20.6 vs 20.5	Any HPV type: 83.8 (61.2 to 94.4) Type 6, 11, 16, or 18: 90.4 (69.2 to 98.1) Type 6: 84.3 (46.5 to 97.0) Type 11: 90.9 (37.7 to 99.8) Type 16: 100 (−420.8 to 100) Type 18: 100 (−3804.6 to 100)	Any HPV type: 60.2 (40.8 to 73.8) Type 6, 11, 16, or 18: 65.5 (45.8 to 78.6) Type 6: 59.4 (31.2 to 76.8) Type 11: 76.3 (40.8 to 92.0) Type 16: 70.3 (−15.5 to 94.7) Type 18: 33.9 (−476.7 to 94.5)	89.4 (65.5 to 97.9)	67.2 (47.3 to 80.3)
Coskuner et al., 2014 [10]	91 vs 81	32.1 vs 36.3	–	–	Non-significant§	
Mikamo et al., 2019 [9]	483 vs 485	22.6 vs 22.6	–¶	–¶	–¶	
Goldstone et al., 2022 [6]	936 vs 867	21 vs 20†	HPV6, 11, 16, or 18: 91.8 (69.4 to 98.6)†	HPV6, 11, 16, or 18: 78.9 (53.9 to 91.2)†	External genital warts related to HPV 6 or 11: 90.4 (62.3 to 98.4)†	External genital warts related to HPV 6 or 11: 81.8 (55.9 to 92.6)†

**Vaccine group vs placebo group. †Early vaccination group (received one or more doses of the quadrivalent HPV vaccine in the base study) vs 'catch-up' vaccination group (placebo recipients who were offered the three-dose quadrivalent HPV vaccine at the end of the base study). ‡No case of cancer for vaccine and control groups. §Men with genital warts after the initial treatment intervention (local excision with electrocautery in larger pedunculated lesions or electrocautery alone in flat broad-based lesions). Vaccination status (P = 0.454) was not independent covariate in multivariate analysis for wart recurrence. ¶No case of HPV-related EGL in both vaccination and placebo groups during follow-up.*

Discussion

Human papillomavirus is a frequent infection in men, leading to various men's health issues. While the beneficial value of HPV vaccination on women's health has been well assessed and communicated, less is known about the efficacy of HPV vaccines in preventing male genital diseases. This systematic review highlights the efficacy of early three-dose quadrivalent HPV vaccination in preventing HPV infections and its sequalae such as EGLs in males. While the low incidence of HPV-related pre-malignant and malignant EGLs limits our ability to evaluate the HPV vaccine's effectiveness in preventing these serious conditions, this limitation is also apparent in the few non-randomised studies assessing the efficacy of HPV vaccination in preventing male genital malignancies [13,14]. Olsson et al. [13] assessed the long-term effectiveness of the nine-valent HPV vaccine in boys aged 9–15 years and reported no cases of HPV-related high-grade genital intraepithelial neoplasia during a median follow-up period of 7.6 years. Therefore, when making the case for HPV vaccination specifically for the prevention of penile cancer, it is challenging to achieve the same level of clarity regarding benign lesions and persistent infections.

Moreover, while the HPV vaccine shows potential in reducing persistent genital HPV infections, we found that data on secondary prevention to prevent recurrence offered as an initial treatment for HPV warts are not convincing through to date. This underscores the importance of early vaccination for males to enhance the efficacy of the HPV vaccine in reducing primary infections and, consequently, the potential transmission to partners. However, the optimal age for vaccination, the ideal number of doses, and the appropriate intervals need to be defined more precisely for males to support HPV vaccination recommendations for the general population.

Conclusion

In light of the benefits and limitations of HPV vaccination in males, future RCTs should focus on defining the optimal age for vaccination and male cancer endpoints in a high-risk population. Moreover, the value of HPV vaccination in participants already infected or at risk of developing diseases related to other HPV types not included in the HPV vaccine needs investigation to guide real-world clinical challenges. Furthermore, future research should be powered to investigate the efficacy of HPV vaccination in preventing male HPV-related external genitalia malignancies.

Disclosure of Interests

The authors declare that they have no conflict of interest.

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PIN lesions		Penile/ perianal/ perineal cancer	Persistent infection		Follow-up
PPP	ITP		PPP	ITP	
All PIN: 100 (−141.2 to 100). PIN Grade 1: (100 (−431.1 to 100). PIN Grade 2 or 3: 100 (−3788.2 to 100)	All PIN: −19.2 (−393.8 to 69.7). PIN Grade 1: 25.6 (−339.9 to 81). PIN Grade 2 or 3: −48.9 (−1682.6 to 82.9)	–‡	Type 6, 11, 16, or 18: 85.6 (73.4 to 92.9) Type 6: 88 (66.3 to 96.9) Type 11: 93.4 (56.8 to 99.8) Type 16: 78.7 (55.5 to 90.9) Type 18: 96 (75.6 to 99.9)	Type 6, 11, 16, or 18: 47.8 (36.0 to 57.6). Type 6: 44.7 (24.1 to 60.1) Type 11: 59.4 (25.7 to 78.8) Type 16: 46.9 (28.6 to 60.8) Type 18: 56.0 (28.2 to 73.7)	Median: 2.9 years
–		–	–		Mean: 46.1 months
–¶		–¶	Type 6, 11, 16, or 18: 85.9 (52.7 to 97.3) Type 6: 86.1 (−8.6 to 99.7) Type 11: 100 (−136.9 to 100) Type 16: 71.4 (−50.0 to 97.1) Type 18: 100 (−6.5 to 100)		36 months
–	–	–	–	–	Median: 10 years vs 5.2 years†

References

1 **Bruni L**, **Albero G**, **Rowley J et al.** Global and regional estimates of genital human papillomavirus prevalence among men: a systematic review and meta-analysis. *Lancet Glob Health* 2023; 11: e1345–62

2 **Das S**, **Doss CGP**, **Fletcher J et al.** The impact of human papilloma virus on human reproductive health and the effect on male infertility: an updated review. *J Med Virol* 2023; 95: e28697

3 **Kranz J**, **Bartoletti R**, **Bruyère F et al.** European association of urology guidelines on urological infections: summary of the 2024 guidelines. *Eur Urol* 2024; 86: 27–41

4 **Leung SOA**, **Akinwunmi B**, **Elias KM**, **Feldman S**. Educating healthcare providers to increase human papillomavirus (HPV) vaccination rates: a qualitative systematic review. *Vaccine X* 2019; 3: 100037

5 **Page MJ**, **McKenzie JE**, **Bossuyt PM et al.** The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; 372: n71

6 **Goldstone SE**, **Giuliano AR**, **Palefsky JM et al.** Efficacy, immunogenicity, and safety of a quadrivalent HPV vaccine in men: results of an open-label, long-term extension of a randomised, placebo-controlled, phase 3 trial. *Lancet Infect Dis* 2022; 22: 413–25

7 **Giuliano PAR**, **Palefsky MJM**, **Goldstone MS et al.** Efficacy of quadrivalent HPV vaccine against HPV infection and disease in males. *N Engl J Med* 2011; 364: 401–11

8 **Lei J**, **Ploner A**, **Elfström K et al.** HPV vaccination and the risk of invasive cervical cancer. *N Engl J Med* 2020; 383: 1340–8

9 **Mikamo H**, **Yamagishi Y**, **Murata S et al.** Efficacy, safety, and immunogenicity of a quadrivalent HPV vaccine in Japanese men: a randomized, phase 3, placebo-controlled study. *Vaccine* 2019; 37: 1651–8

10 **Coskuner ER**, **Ozkan TA**, **Karakose A**, **Dillioglugil O**, **Cevik I**. Impact of the quadrivalent HPV vaccine on disease recurrence in men exposed to HPV infection: a randomized study. *J Sex Med* 2014; 11: 2785–91

11 **Saunders CL**, **Meads C**, **Abel GA**, **Lyratzopoulos G**. Associations between sexual orientation and overall and site-specific diagnosis of cancer: evidence from two national patient surveys in England. *J Clin Oncol* 2017; 35: 3654–61

12 **Arroyo Mühr LS**, **Gini A**, **Yilmaz E et al.** Concomitant human papillomavirus (HPV) vaccination and screening for elimination of HPV and cervical cancer. *Nat Commun* 2024; 15: 3679

13 **Olsson S-E**, **Restrepo J**, **Reina J et al.** Long-term immunogenicity, effectiveness, and safety of nine-valent human papillomavirus vaccine in girls and boys 9 to 15 years of age: interim analysis after 8 years of follow-up. *Papillomavirus Res* 2020; 10: 100203

14 **Swedish KA**, **Factor SH**, **Goldstone SE**. Prevention of recurrent high-grade anal neoplasia with quadrivalent human papillomavirus vaccination of men who have sex with men: a nonconcurrent cohort study. *Clin Infect Dis* 2012; 54: 891–8

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Abbreviations: EGL, external genital lesion; HPV, human papillomavirus; ITP, intention-to-treat population; PIN, penile intraepithelial neoplasia; PPP, per protocol population; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial.

