Systematic Review

Prevalence and distribution of human papillomavirus (HPV) serotypes of the anogenital region in adolescent boys and young men: a systematic review

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ABSTRACT

The objective of this study is to investigate the impact of HPV vaccinations on the prevalence of HPV serotypes on adolescent boys and young men through a systematic review. The search aimed for clinical studies in English up to 2022 concerning HPV serotyping of samples from randomly selected, non-high risk male participants, aged 11-25 with no underlying pathologies. The search resulted in 18 eligible articles among which 15 concerned un-vaccinated and 3 concerned vaccinated young males. In 4 articles the participants were homosexual/bisexual, in 4 they were heterosexual while in the rest of the publications the sexual orientation of participants was mixed or unspecified. In about half of the articles, sample collection predated the initiation of national HPV vaccination programs for girls in the respective countries. In the selected articles, HPV seroprevalence varied significantly depending on vaccination rates and variability in methodology. Overall HPV prevalence was found to be high in most studies. Significant reduction of HPV vaccine-type prevalence was detected only in directly vaccinated adolescent boys and young men.

Key Words: HPV; adolescent boys; HPV vaccine; seroprevalence

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Introduction

The Human Papilloma Virus (HPV) is the most widespread sexually transmitted infectious agent, which is responsible for causing a variety of skin and epithelial lesions in the anogenital area of males and females, including precancerous lesions and carcinogenesis (1). The HPVs are categorized in high- or low-risk types based on their tumorigenicity. Types 6, 11, 40, 42, 43, 44, 54, 61, 72, 81 are considered low-risk, non-oncogenic types and are usually responsible for low-grade histological lesions such as papillomas and warts. Among the high-risk oncogenic types are types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82 which can potentially cause high-grade histological lesions leading to cancers such as cervical and other procto-genital cancers as well as oropharyngeal cancers (2). It is estimated that 4.5% of all new cancer diagnoses are related to HPV infection. Cervical cancer constitutes 83% of these cases, while the largest percentage concerns women in low-income countries (3). Considering these findings, increased surveillance of HPV infections and systematic research on prevention strategies including the enhancement of vaccination programs are imperative.

Despite the availability of approved HPV vaccines since 2006-7 and their inclusion in national vaccination programs in over 107 of the 194 WHO member states as of June 2020, global vaccination coverage still remains low (4). However, even in countries where vaccination coverage does not exceed 50%, it has been found that vaccinations appear to reduce the prevalence of HPV and the rates of HPV-related neoplasms (5). In particular, according to the recent Cochrane systematic review on the efficacy and safety of vaccination of adolescent girls and young women up to 26 years of age, HPV vaccines were found to be highly effective in preventing cervical precancerous lesions (6). Therefore, the systematic investigation of vaccination protocols for their optimization as well as the identification of factors that may inhibit vaccination coverage is necessary.

The available prophylactic vaccines against HPV are the bivalent vaccine targeting HPV types 16, 18, the quadrivalent vaccine against types 6, 11, 16, 18 and the ninevalent vaccine against types 6, 11, 16, 18, 31, 33, 45, 52, 58 (7). According to the original WHO guidelines and protocols, national vaccination programs primarily targeted adolescent girls who are at 10 times higher risk of malignancy due to HPV infection than boys, while protection to boys should incur through herd immunity (8). Herd immunity effects though, have been detected only in countries with very high vaccination coverage of women (9). Therefore, current studies on the effectiveness of herd immunity tend to emphasize on the need to expand vaccination programs so that they also include boys (9). Another argument for the need of a pangender vaccination approach is that even if herd immunity is developed, vaccinating women does not offer any protection to homosexual men (10). Moreover, the prevalence of HPV-related head and neck cancers is much higher in men than in women although the HPV types that are associated with the development of such cancers are included in the available vaccines (11). In several countries vaccination programs that also include adolescent boys are already implemented (12), while further systematic research on the necessity of pangender vaccinations in order to reduce the risk of HPV-related neoplasms, especially in males, is deemed necessary (13).

Considering the aforementioned, the need for systematic research on the restructuring and promotion of HPV vaccination programs that ensure adequate coverage of the male population is imperative. In this context, the main purpose of this systematic review is to investigate the effect of vaccination programs on the prevalence of different HPV types in adolescent boys and young men. The ultimate goal of this study is to evaluate the prevalence of HPV in the male population as well as the degree of protection provided to them through herd immunity due to the vaccination of girls. The results of the review will be discussed with a view to assessing the need to include adolescent males in national HPV vaccination programs.

Materials and Methods

The main aim of this systematic review was to investigate the effect of current vaccination programs on the prevalence of the various HPV types in adolescent boys and young men, emphasizing on the vaccine types. More specifically, the present study aimed to investigate fluctuations in the overall prevalence and distribution of HPV subtypes in males aged 11 to 25 years. The search for relevant articles was performed without a time limit until 12/2022 in order to select articles before and after 2006, when global HPV vaccination programs initiated. Possible changes in the distribution of HPV subtypes were examined in relation to the time of initiation of nation-

al vaccination programs in the country where each selected study was conducted, but also in relation to the age and sexual orientation of the participants. The main research question in this study is whether herd immunity resulting from vaccination of females also protects the male population or whether direct vaccination of boys is necessary. It is a research hypothesis that in studies conducted in countries where national vaccination programs for girls were implemented prior to the time of the study, the prevalence of HPV may also be different in men compared to studies conducted in unvaccinated female populations. Another research hypothesis is that the overall prevalence in male populations should show a decreasing trend in order to consider that vaccination programs so far have offered some degree of protection to males.

The search and selection of articles for this systematic review was performed in accordance with the PRISMA guidelines (14). Articles were searched through the international database PubMed based on the algorithm (HPV OR "human papilloma virus") AND (adolescent OR teens) AND (serotypes OR types) AND (boys OR men OR male). According to the advanced search options of this database, only articles in the English language were retrieved. The eligibility of the retrieved articles was assessed in accordance to specific inclusion criteria. According to these criteria, eligible articles should exclusively include studies in a human model (cohort, observational, cross-sectional, etc.) and be conceptually compatible with the purpose of the study. The articles should concern male participants aged 11 to 25 years without diagnosed underlying pathological or infectious diseases such as neoplasms or HIV. Moreover, articles should concern randomly selected participants and not high-risk groups for HPV such as people with dermatological lesions and warts or people whose partners have been diagnosed with HPV. Finally, articles should present quantitative HPV serotyping data using the PCR method on anogenital swab samples or from urine samples. The references of the selected articles were also assessed for eligibility.

Results

The initial search through the PubMed database yielded 1133 which were then assessed against the aforementioned selection criteria according to the PRISMA specifications. As presented in the flow chart in figure 1, 642 articles were excluded due to obvious inconsistency with the objective of the study or for comprising literature reviews, meta-analyses, *in vitro* studies or studies in a non-human model. A further 473 articles were excluded as they did not refer to males or the required age group or concerned high-risk participants or their sampling and serotyping methods were not compatible to the inclusion criteria of this study. The final number of selected articles that met the selection criteria was 18 (Figure 1). After examining the references of the selected articles, no additional articles were identified as the articles that met the search criteria were duplicates of those already selected during the initial search.

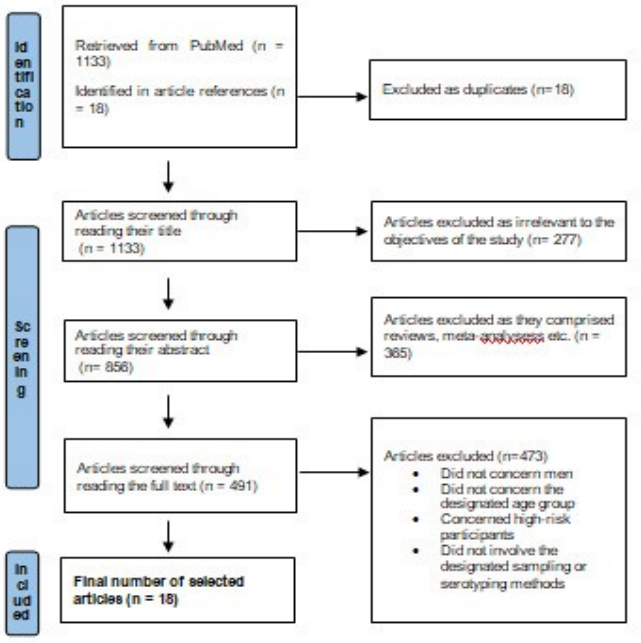

Figure 1. Flow chart of article selection according to PRISMA guidelines

The 18 selected articles included 4 cross-sectional studies, 11 observational studies, 1 randomized clinical trial and 2 cohort studies (Table 1). The studies in the selected articles date from 2004 to 2021 as no earlier studies were found that met the selection criteria. The selected studies involve participants from geographical areas of all continents. Regarding the purpose of τηε them aim to evaluate the prevalence of HPV and the factors that increase the risk of HPV infection. Among the selected studies, 10 exclusively examined HPV prevalence in male participants and 8 in male and female populations. The majority of studies (15) involved unvaccinated participants, 1 study involved vaccinated participants (15) while 2 studies included both vaccinated and unvaccinated participants(16; 17). In the majority of studies, the sexual orientation of the participants is not mentioned or considered, while 4 studies specifically examine men who have sex with men and 4 specifically examine heterosexual men (Table 2). Concerning sampling methods, in

5 studies HPV serotypes were identified in urine samples (17; 18; 19; 20; 21) while in the remaining 13 swab samples from the anogenital region were used. Another observation is that in 9 studies the start of the national vaccination program for girls in the country where the study was conducted was contemporary or later than the time of the study while in the other 9 it was earlier (Tables 3, 4).

An initial observation regarding the results of the studies is that in the studies where HPV serotypes were identified in a urine sample the range of rate values recorded was approximately sub-tenfold of the rates identified from anogenital swabs (Figure 2). It is therefore questionable whether the two sampling methods have comparable sensitivity as current literature suggests that HPV detection in men's urine is not as effective as detection in anogenital swabs (22). Regarding the age of the participants in the selected articles, it ranges from 11 to 25 years. In the context of this systematic review, it was considered appropriate to investigate the prevalence of HPV in this age range, considering the fact that the initiation of sexual activity in adolescence significantly increases the prevalence of HPV, while the maximum effects of this increase are detected in early adolescence (23).

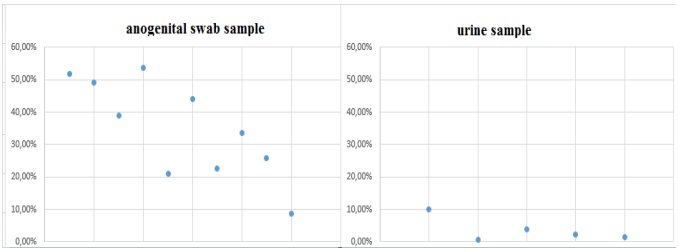

Figure 2 Indicative values of total HPV prevalence from the selected articles in anogenital swab and urine samples

Among the selected articles, examining overall HPV prevalence and high- and low-risk subtypes separately for adolescent and early adolescent age groups, Sonnenberg *et al.*, (2013) (19) and Gargano *et al.*, (2017) (15) detected significant increase in early adolescence. In addition, Sonnenberg et al., (2013) (19) point out that in men this increase remains constant while in women it decreases, an observation consistent with the fact that the virus has different behavior and resistance between the two sexes (24). Similar conclusions are reached by O'leary *et al.*, (2011) (21), according to which the prevalence of the virus is significantly higher in the age group of 15-18 years compared to the age group of 11-14 years, so the proposed age to start vaccination she should be younger than 15 years old. Accordingly, Hussain *et al.*, (2012) (20) and Bianchi *et al.*, (2013) (18), estimate that the prevalence of HPV in boys under 13 years is minimal. A safe conclusion that is consistent with the current literature is that the optimum vaccination age of boys should be early adolescence in order to prevent an increase in the prevalence of the virus in adolescence and post-adolescence with the onset of sexual activity (23).

Regarding studies that included vaccinated participants (15; 16; 17), although limited, they conclude that direct vaccination of boys significantly reduces HPV prevalence . These findings clearly demonstrate the effectiveness of direct vaccination of young boys in reducing HPV infections as seen in current studies conducted in countries implementing widespread or pilot vaccination programs in men who have sex with men (25) but also in random populations of males (26). According to the same studies, however, these programs should be expanded in order to offer adequate protection to boys and young men. Regarding the sexual orientation of the participants, as mentioned above 4 studies specifically examine men who have sexual contacts with men as the population of these men has a higher HPV prevalence than heterosexual men (27). Both Chow *et al.*, (2021) (16) and Zou et al. (2016) (28) found a significantly higher prevalence of low-risk vaccine subtypes (6, 11) than high-risk subtypes (16, 18) possibly related to differences in subtype prevalence by site of infection as in anal HPV infections low-risk types are more common in men who have sex with men (28). Zou *et al.*, (2014) (28) detect a high prevalence of both high- and low-risk subtypes included in the 4v vaccine and highlight the need for prophylactic vaccinations at a fairly young age as the increase in viral prevalence is rapid with the onset of sexual activity of MSM boys.

Nyitray *et al.*, (2011) (29) also found that HPV prevalence is higher in men who have sex with both women and men compared to exclusively gay and heterosexual men. They further pointed out that the distribution of subtypes and the factors influencing the prevalence of oncogenic types are different for heterosexual men (30). Regarding the selected articles that deal exclusively with heterosexual men, HPV prevalence is also high while Partridge et al. (2007) (31) also pointed out that the rate of occurrence is higher than in women, a fact that should be taken into account when planning vaccination programs. Accordingly, Vardas et al. (2011) (32) in an observational study of heterosexual

Table 1: Methodology and results of selected articles

	article	#participants	age	vaccination status	sampling method	total HPV prevalence	prevalence of high-risk types	prevalence of low-risk types (6, 11)	16 or 18	16 or HPV 6, 11, 18, 31	Remarks/Scope/Conclusions
1	Chow et al., 2021	177	18,7 +/- 1,3	dp	anogenital swab			10, 17 vs.	5, 36 vs.	1 1,6,66	
	Chow et al., 2021	139	18, 841	un	anogenital swab			4, 47 vs.	1 46 vs.	6, 1 vs.	Diverse widespread rates of the same low-HPV types in vaccinated boys but higher prevalence of these risk types in both groups
3	Wendland et al., 2020	1130	18,5 ±	dp	anogenital swab	9 1,9 Oo.	3 +1, 30 vs.				High HPV prevalence with different distribution of vaccine-related genotypes between sexes
5	Wittawatmongkol et al., 2019	67	16 (17 - 21)	dp	anogenital swab	4 9vs.	3 6vs.				High prevalence of HPV; higher in HIV positive. CIN lesions positive for HPV; HR types were detected in 18% while LR types in 4% and 16 were detected in 3 cases.
6	Lehtinen et al., 2017	5 96	1 A	un	urine	4, 1 Oo.	2,5 Oo.	0, 80 vs.	0 vs.		Significant decrease in HPV prevalence 4 years after vaccination
	Lehtinen et al., 2017	1 80	1 A	dp	urine	1 0, 1 Oo.	0vs.	1, 40 vs.	2, 10 vs.		
8	Gargano et al., 2017	1 4 - 1 6 y: 42 3 20 - 24 y: 3 34	1 4 - 1 6 y 20 - 2 4 y	un	anogenital swab	1 4 - 1 6 y: 12, 8vs. 20 - 24 y: 18, 3vs.	1 4 - 1 6 y: 7, 3vs. 20 - 24 y: 9 vs.		1 4 - 1 6 y: 1, 8 vs. 20 - 24 y: 2, 7 vs.	1 4 - 1 6 y: 1, 8vs. 20 - 24 y: 6vs.	Differences in the prevalence of the 6 vaccine types compared to the non-self-perceived exaggerate detrimental effect of HPV vaccination on the whole
6	Zou et al., 2016	2 00	1 6 oo: 2 0	dp	anogenital swab			1 8, 50 vs.	6, 50 vs.		The proportion of men positive for types 6/11 was significantly higher than for types 16/18 (All ORs vs. R; Bonf. p < 0.001)
7	Zou et al., 2014	2 00	1 6 oo: 2 0	dp	anogenital swab	5 0vs.	3 1vs.	10, 50 vs.			The prevalence of HPV in all 5 types, including the 4 vaccine types, increased rapidly with the onset of sexual activity, suggesting that vaccination should be initiated at a fairly young age.
8	Bianchi et al., 2013	5 03	11 - 14: y 10, 2 15 - 18 y 7, 50	dp	urine	11 - 14: y 0, 6 vs., 15 - 18 y 0, 3 vs.					1 male HPV prevalence, almost consistent with the data regarding the 12 NQ vaccine from sexually active boys not vaccinated, thus underscoring the importance of the latter's vaccination
9	Sonnenberg et al., 2013	information not synthesized yet	16 1 7y 18 - 19y 20 - 24 y	dp	urine		1 6, 17 y: 4, 9vs. 18, 19 y: 8vs. 20 - 24 y: 6, 8vs.		16, 17 y: 0, 6vs. 18, 19 y: 0, 4vs. 20 - 24 y: 2, 7 vs.		HPV prevalence is higher in young women who have never had intercourse with regular sexual activity, requiring reliable information
10	Vriend et al., 2012	450 (16 - 18 y: 92; 19 - 21 y: 168; 22 - 24 y: 190)	1 6 oo: 2 4	dp	anogenital swab	9 3, 7 Oo.	3 9, 90 vs.	18, 60 vs.			High prevalence of HR-HPV infection in women
11	Hussain et al., 2012	3 40	16 oo: 17 (1 5 6 of 2 7 5)	dp	urine	2 1 vs. 1 1 years	0				Very low HPV prevalence
12	O'Leary et al., 2011	7 3 6	1 1 oo: 1 8	dp	urine	11 - 14: y 1 6 vs., 15 - 18 y 5 0 vs.	11 - 14: y 1 vs., 15 - 18 y 2, 8 vs.	11 - 14 years: 0, 6 vs. 15 - 18 years: 1, 6 vs.	11 - 14 years: 0, 3 vs. 15 - 18 years: 0, 7 vs.		HPV prevalence in ages 11 - 14, which is before recommended age group for vaccination, is lower than 15 - 18. The prevalence of the latter, in boys, requires further investigation
13	Vardas et al., 2011	3 1 3 3	15 - 26 (mean: 20 2 1)	dp	anogenital swab	3 1 vs.		3, 3 vs.	0, 6 vs.	0, 6 vs.	The prevalence of HPV of all types is quite high among women likely under or before sexual young years. The highest prevalence was found in 18 - 20 years and the lowest in 26 - 30 years. Cervical cancer or abnormalities do not appear to affect the prevalence of the virus.
14	Nyitray et al., 2011	6 9 6	1 8 2 4	dp	anogenital swab	4 4vs.	3 9vs.				HPV prevalence is higher in MSM than in MSW and MSC. However, the distribution of subtypes and the factors influencing the prevalence of oncogenic types are not different in the MSM.
	Nyitray et al., 2011	9 7	1 8 2 4	dp	anogenital swab	6 2vs.	3 4vs.				
15	Parada et al., 2010	4 0	1 8 2 4	dp	anogenital swab	3 2, 5 Oo.					The prevalence of HPV in men was consistent with global estimates, as for whom the prevalence in women was also similar. However, the number of sexual partners was a risk factor in the study for the acquiring the risk of HPV infection.
16	Giuliano et al., 2008	1 8 2 0 (y: 1 7 - 2 1: 3 9; y 1 6 - 2 6: 1 7 8)	16 - 26, 21 - 26	dp	anogenital swab	1 8 2 0 4 6 vs. 21 - 26: 2 7 vs.	16 - 26 vs. 21 - 26: 2 1 vs.	16 - 26 vs. 21 - 26: 2 1 vs.			The prevalence of HPV in men was found to be high, with a decline but a persistence of infection and clearance.
17	Partridge et al., 2007	2 4 0	1 8 2 6	dp	anogenital swab	3 9, 6 Oo.	3 0 vs.	1 0 vs.			The prevalence of HPV in men was found to be high, and at a higher rate of recurrence in than in female population of harmony, a fact that should offer to him intervention when planning vaccination programs.
18	Shin et al., 2004	5 8 1	median 2 3	dp	anogenital swab	8, 7 Oo.	4, 7 Oo.	3, 6 Oo.			HPV prevalence is higher in women but HR-HPV types prevalence is close in both sexes

Table 2: Sexual orientation of participants in each study

	article	sexual orientation
1	Chow et al., 2021	MSM
2	Wendland et al., 2020	
3	Wittawatmongkol et al., 2019	
4	Lehtinen et al., 2017	
5	Gargano et al., 2017	
6	Zou et al., 2016	MSM
7	Zou et al., 2014	MSM
8	Bianchi et al., 2013	
9	Sonnenberg et al., 2013	
10	Vriend et al., 2012	
11	Hussain et al., 2012	
12	O'Leary et al., 2011	
13	Vardas et al., 2011	MSW
14	Nyitray et al., 2011	MSW
	Nyitray et al., 2011	MSM
15	Parada et al., 2010	MSW
16	Giuliano et al., 2008	
17	Partridge et al., 2007	MSW
18	Shin et al., 2004	

Table 3: Studies conducted prior to the initiation of a national vaccination program

article	study conducted in:	initiation of national vaccination program in:
Wittawatmongkol et al., 2019	2013 - 2014	2017
Vriend et al., 2012	2009	2010
Hussain et al., 2012	2011??	2016
Vardas et al., 2011	<2011	>2011
Nyitray et al., 2011	2005-2009	2006,2012,2014
Nyitray et al., 2011	2005-2009	2006,2012,2014
Parada et al., 2010	2002-2003	2012
Giuliano et al., 2008	2003-2005	2006
Partridge et al., 2007	2003-2006	2006
Shin et al., 2004	2002	2016

Table 4: Studies conducted after the start of a national vaccination program

article	study conducted in:	initiation of national vaccination program in:
Chow et al., 2021	2010-2012	2007
Chow et al., 2021	2010-2012	2007
Wendland et al., 2020	2016-2017	2014
Lehtinen et al., 2017	2010 - 2014	2007-2009
Lehtinen et al., 2017	2010 - 2014	2007-2009
Gargano et al., 2017	2013 - 2014	2006
Zou et al., 2016	2010 - 2012	2007
Zou et al., 2014	2010 - 2012	2007
Bianchi et al., 2013	2009 - 2010	2007-2008
Sonnenberg et al., 2013	2010 - 2012	2008
O'Leary et al., 2011	2008	2008

men on 5 continents found a high prevalence of all HPV types while pointing out that the prevalence of the virus did not seem to be affected by condom use or circumcision.

Likewise, Parada et al. (2010) (33) found the HPV prevalence of heterosexual young men in Mexico to be high and directly related to the prevalence in women, while the number of sexual partners was considered to be the main factor increasing the risk of HPV infection. A high prevalence was also observed in studies involving a random population of boys and young men selected regardless their sexual behavior. Thus, Wendland *et al.*, (2020)(34) και Wittawatmongkol *et al.*, (2019) (35) estimated an overall HPV prevalence of approximately 50% while the prevalence of high-risk types was approximately 30%. Wendland et al. (2020) (34) also detected a different distribution of the 4v vaccine subtypes between men and women, which does not support the theory of herd immunity. Giuliano *et al.*, (2008) (36) also pointed out that in young men the rate of infection and clearance is faster than in women. These results are consistent with international studies according to which the prevalence of HPV in men, the persistence of infection and the immune responses vary according to their sexual behavior (30).

Regarding the analysis of results in relation to the vaccination coverage of women, the prevalence of the high- and low-risk subtypes included in the vaccines did not appear to differ significantly in studies where the initiation of the national girls' vaccination program in the study country preceded the study comparing to studies that were implemented prior to the initiation of the respective vaccination programs. Moreover, across all the selected articles, the overall prevalence of HPV remains high among young sexually active men, regardless of women's vaccination coverage. The direct vaccination of young boys seems to have a significant effect on the prevalence of oncogenic and non-oncogenic HPV subtypes, while the design of unified national vaccination programs regardless of gender and sexual orientation may be the most effective approach to limiting HPV infections and their effects.

Discussion

Most of the studies on HPV in the current literature concern the diagnosis, treatment, and prevention of HPV infections in women. Accordingly, most health programs for the epidemiological control and prevention of HPV focus on women, while the role of men in the epidemiology of the virus tends to be overlooked. Consequently, studies focusing on the epidemiology and prevention of HPV in young men are limited and their results inconclusive. In addition, a large percentage of research on the epidemiology of HPV in men specifically concerns men who have sex with/and with men as they are a population group with a high prevalence of HPV that does not benefit from possible herd immunity due to vaccination of girls (10). Given the fairly high prevalence of the virus in men as well as the fact that men are often asymptomatic carriers and contribute to the spread of the virus by increasing the burden of the consequences of HPV infections in women, further systematic investigation of the epidemiology of HPV in men is deemed imperative (37).

According to this systematic review, it is concluded that the prevalence of the virus in adolescent and young male populations worldwide remains high. No changes in the prevalence of the HPV subtypes included in the vaccines were observed, which would imply herd immunity effects, while a significant reduction in overall virus prevalence was observed only in studies that included directly vaccinated boys (15;16;17). This observation is consistent with relevant recent studies confirming the reduction of HPV infection rates in vaccinated young boys which advocate the need to include young boys in national vaccination programs (10). Moreover, according to the relevant literature, reduction in the prevalence of high-risk HPV types in men has only been observed in countries with particularly high vaccination coverage of women (9;38). For example, according to a study in Britain where the vaccination coverage of girls exceeds 80%, a significant reduction was also observed in the rates of HPV infections of the oropharynx in men as a result of herd immunity (39).However, in the majority of studies on the effectiveness of herd immunity, it is found that it does not provide sufficient protection while the need to expand vaccination programs to young boys is highly emphasized (40).

Another observation to be discussed in this systematic review concerns the age of boys at which HPV prevalence increases rapidly as a result of the initiation of sexual activity and which should be the age limit for immunizing young boys. According to the results of the selected articles, an increase in the prevalence of the virus is observed in the age groups above 14 years, while in boys up to 13 years the prevalence of HPV is particularly low (20;21). Consequently, the ideal age for boys to be immunized is earlier than 13-14 years whi

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