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ORAL HUMAN PAPILLOMAVIRUS IN MEN WHO HAVE SEX WITH MEN IN LATIN AMERICA: A REVIEW

M.R.B. GUAPILLO-VARGAS[1], J. JARAMILLO-VÁZQUEZ[2], B.I. CERDA-CRISTERNA[3]

[1]School of Chemistry Sciences, Universidad Veracruzana, Región Orizaba-Córdoba, Orizaba, Veracruz, México
[2]Mendoza Health Center, Secretaría de Salud del Estado de Veracruz, Mendoza, Veracruz, México
[3]School of Dentistry, Universidad Veracruzana, Región Orizaba-Córdoba, Río Blanco, Veracruz, México

Corresponding Author
Bernardino Isaac Cerda-Cristerna, DDS, MSC, PhD; e-mail: bcerda@uv.mx

ABSTRACT – *Objective:* Men who have sex with men run a high risk of oral human papillomavirus, and studies have investigated its prevalence in Latin America. It is important to know the public health challenges that the region faces regarding oral human papillomavirus and its association with oropharyngeal cancer. Thus, the aim of this study was to review the status of oral human papillomavirus in men who have sex with men in Latin America.

Materials and Methods: We reviewed studies involving cohorts of men who have sex with men in Latin American countries.

Results: The prevalence of oral human papillomavirus in men who have sex with men ranged from 14.3% to 94.5% according to studies performed in Latin American countries. In those countries, the oral human papillomavirus genotypes were mostly HPV-16 and HPV-58. The prevalence of the infection is higher in men living with HIV and having sex with men than in heterosexual men and in men without HIV having sex with men.

Conclusions: Oral human papillomavirus in men who have sex with men is a major challenge in Latin America. Social policies to prevent, diagnose, and treat the oral human papillomavirus infection in men who have sex with men need to be developed and applied.

KEYWORDS: Latin America, Human papillomavirus, Oral cancer, Prevalence.

INTRODUCTION

Human papillomavirus (HPV) is a virus transmitted by sexual contact. The World Health Organization (WHO) estimates that all sexually active women and men will acquire HPV during their lives[1]. The infection occurs in the skin or mucosa because the virus has epithelial tropism, and, as a result might infect the oropharyngeal mucosa. The oral HPV infection can cause oropharyngeal cancer (OPC), a malignant disease occurring in countries around the world, including in Africa, Asia, Europe, the Middle East, North America, and South America[2-4]. A worldwide increase in OPC associated with HPV has occurred in recent years[4]. The OPC associated with HPV is an oncologic factor for both men and women, but some groups are more vulnerable than others. Men who have sex with men (MSM) and living with human immunodeficiency virus are prone to HPV infection because their behavior can expose them to risks associated with the HPV infection and because the HIV immunosuppressive condition favors coinfection[5-14].

HPV is a member of the *Papillomaviridae* family, which includes 200 types of HPV classified by oncogenic ability[15,16]. Low-risk HPV (LR-HPV) includes types HPV 6, 11, 40, 42, 43, 44, 54, 61, 72, 81, and CP6108 and is associated with benign lesions[17]. In contrast, high-risk HPV (HR-HPV) includes types HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59[15-17]. The HR-HPV types can persist in the host and are associated with intra-epithelial neoplasia and squamous cell cancer in the cervix, vagina, penis, anus, rectum, and oropharynx. HPV-16 is the type most frequently associated with OPC[18]. HR-HPV types have been associated with OPC, and the prevalence of oral HPV in populations around the world should be investigated.

Studies have reviewed the prevalence of OPC associated with HPV in North America, Europe, and Asia[4,19-21]. However, to our knowledge, the prevalence of oropharyngeal cancer associated with HPV in MSM in Latin America has not yet been reviewed. In Latin America and the Caribbean, 2.5 million people live with HIV, and 48% of them are gay men and other MSM[22]. Moreover, the prevalence of HIV in MSM in Latin American countries is significant. For example, the prevalence is 11.4%, 14.9%, 18.3%, 19.1%, and 20.4%, in Argentina, Mexico, Brazil, Chile, and Colombia, respectively[22]. HIV in MSM is well recognized as a risk factor for HPV, and MSM constitute a group in which oral HPV is present[7,19,23,24]. Reviewing the evidence on oral HPV in MSM in Latin America can help dentists, researchers, health authorities, and policymakers understand the challenge for countries in Latin America and to identify similarities and differences of the situation in other regions of the world. We identified two main questions to guide the review: "What is the prevalence of oral HPV in MSM in Latin-American countries?" and "What are the most frequent types of high-risk oral HPV in MSM in Latin-American countries?" Therefore, the aim of this study was to review the burden of oral HPV in MSM in Latin America.

MATERIALS AND METHODS

We performed a narrative review with a strict search method. Our PICO method was as follows: P: MSM in Latin America, I: identification of oral HPV, C: comparison with a control group of men, and O: oral HPV types and prevalence. Figure 1 shows the PRISMA flow diagram. We searched for studies in the PubMed and Scielo databases using the following keywords: "oral human papillomavirus", "oral HPV", "high risk human papillomavirus", "men who have sex with men", "MSM", and "prevalence". We used Scielo in our search because that tool includes Latin American journals. The search for studies included the combination of those keywords and the name of a Latin-American country. As a country name, we considered the countries and territories listed by Luciani et al[25]: Mexico and Central America – Mexico, Belize, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, and Panama; South America – Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, Peru, Paraguay, Venezuela, and Uruguay; and the Latin Caribbean – Cuba, Dominican Republic, Haiti, Martinique, and Puerto Rico. We included studies in the English language or Spanish language and those published between January 2000 and December 2023. To explore the research question, we included the studies that had a cohort with MSM and that explored the prevalence of oral HPV and/or the prevalence of high-risk oral HPV; when low-risk oral HPV was explored, we also reported the findings. We excluded studies that did not include a MSM group or did not report the prevalence of oral HPV and publications describing a future study on the topic. Two authors performed the search; all authors discussed the evidence shown by the studies.

RESULTS

We found only one study in Scielo and located most of the studies in PubMed. The results showed few studies on oral HPV and MSM in Latin America, and we investigated seven researches (Table 1). One study reported evidence collected in Brazil, one evidence collected in Puerto Rico, four evidence collected in Mexico, and one evidence collected in Peru. As the studies showed different methodologies and outcomes, a narrative review was an adequate first approach to summarizing the studies. All studies included a MSM population, but only four studies reported the prevalence of each type of oral HPV.

Oral HPV infection in MSM

MSM is a population at high risk of oral HPV infection, and, in Latin America, efforts have been made to investigate MSM. In a study done in Brazil, De Souza Vianna et al[26] performed an observational study and found the prevalence of oral HPV to be 14.3% in homosexual men and 20% in bisexual men. In that study,

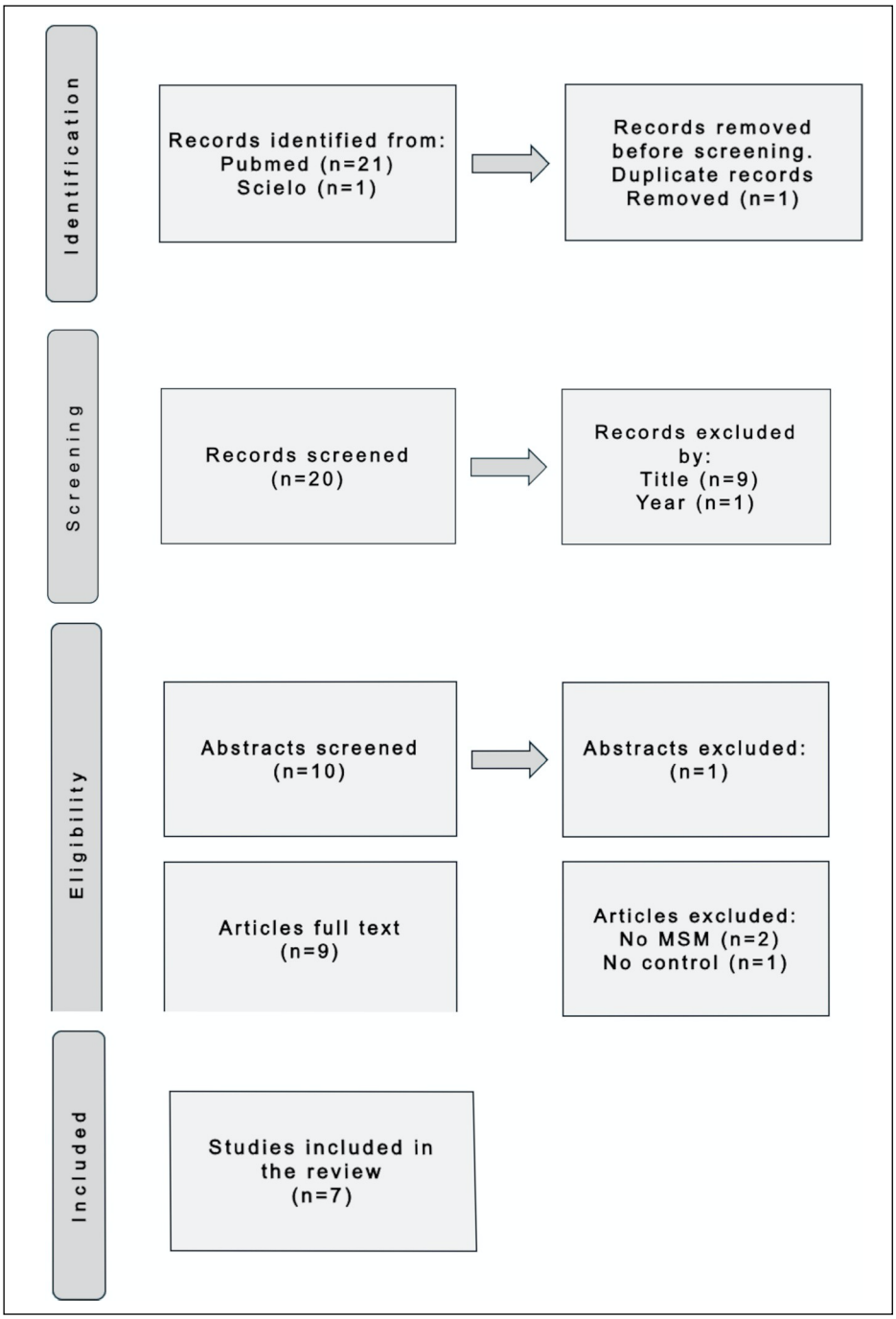

Figure 1. PRISMA flow diagram.

heterosexual men showed a prevalence of oral HPV of 11.1%. In addition, the prevalence of HR-HPV was 9.5%, 10%, and 3.7% in homosexual men, bisexual men, and heterosexual men, respectively[26]. The same authors identified HR-HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) and LR-types (6, 11, 42, 43, 44) but did not report the prevalence for each oral HPV type[26]. Not reporting the prevalence of each oral HPV type was an important limitation of the study as was answering only one of our research questions.

Colon et al[27] performed a cross-sectional study on a group in Puerto Rico with 57 MSM (mean age of 38.5 years, standard deviation 14.2, minimum age range 16-14 and maximum age range 55+) and found the prevalence of oral HPV to be 19.3% but did not report the type of HPV for that population. As the MSM population was part of a cohort of men (n = 205) the study was not focused on the prevalence of HR-HPV or LR-HPV in the MSM population and that information was lacking in the report[27].

Table 1. Studies investigating the prevalence of oral human papillomavirus in men who have sex with men and the techniques used for detection.

Country	Reference	Technique for Collection	VPH Detection Method
Brazil	Vianna et al[26] 2018	No description of the sampling technique.	HPV genotyping by hybrid capture
Mexico	Anaya-Saavedra et al[28] 2013	Disposable punch for tissue	DNA genotyping by HPV16- and HPV18- positive electropherogram
Mexico	Castillejos-García et al[29] 2018	Collection with a cytobrush	DNA genotyping by HPV16- and HPV18-positive electropherogram
Mexico	Carnalla et al[30] 2023	Oral rinse.	DNA detection with real-time polymerase chain reaction (qRT-PCR)
Mexico	Méndez-Martínez et al[31] 2020	Collection with a cytobrush	DNA genotyping by linear array
Peru	Blas et al[32] 2015	Oral rinse	DNA genotyping by linear array
Puerto Rico	Colon-López et al[27] 2014	Oral rinse	HPV genotyping by hybrid capture

In Mexico, Anaya-Saavedra et al[28] performed a cross-sectional study and explored the prevalence of oral HPV in MSM (median age of 33 years, interquartile range (Q_1-Q_3):27-40). The study involved 562 MSM who were part of an HIV positive cohort of 735 men. For the MSM, the prevalence of oral HPV was 9.25% (52/562); however, the study did not report the type of HPV for that population. In another study in Mexico, Castillejos-García et al[29] performed a longitudinal, observational, and analytical study involving 97 participants living with HIV (median age of 36 years, interquartile range (Q_1-Q_3): 29-44), of the total number of participants, 74 were MSM. The authors explored the presence of HPV in the oral and oropharyngeal regions and found that 54 participants (55.7%) showed oral HPV and oropharyngeal HPV and that 43 participants (44.3%) showed no oral HPV[29]. However, an important limitation of that study was that the data reported by the authors did not show the prevalence of oral HPV only for MSM. For all the participants, the prevalence of HPV-18 types 58 and 16 were 24.1%, 13%, and 1.9%, respectively[29]. Also in Mexico, Carnalla et al[30] performed a cross-sectional study involving 485 MSM. The study estimated the prevalence of oral HPV and reported a prevalence of HR-HPV of 11.1%. Moreover, the prevalence of oral HPV was 14.8% for HIV-positive MSM (n = 196) while the prevalence of oral HPV was 8.7% for MSM without HIV (n = 289), with significant statistical differences (p = 0.03). The HR-HPV types 56/59/66 were those most identified (4.9%) while the prevalence of HPV-16 was 1.4 % (95% CI:0.7-2.9)[30]. In Mexico also, Méndez-Martínez et al[31] performed a cross-sectional study involving 102 HIV-positive MSM (median age of 38.4 years ± 8 years; age range 21-61 years), who had previously participated in a study in which they were identified as HPV-16 positive in the anal canal. The study explored the prevalence of oral HR-HPV and oral LR-HPV. The prevalence of HPV-16, HPV-39, HPV-18, HPV-52, HPV-51, HPV-66, and HPV-68 was 80.4%, 61.8%, 52.9%, 49.0%, 38.2%, 33.3%, and 13.7%, respectively. The prevalence of HPV-11, HPV-6, HPV-70, and HPV-44 was 53.9%, 34.3%, 3.9%, and 1%, respectively[31]. Because all the participants were identified as having HPV-16, the prevalence of oral HPV for all of them was 100%.

In a study performed in Peru, Blas et al[32] studied an MSM cohort and reported that the prevalence of oral HPV was 44.3% in HIV-positive MSM and 22.4% in HIV-negative MSM (p = 0.04). The prevalence of HR-HPV was 27% in HIV-positive MSM and 15% in MSM, specifically the prevalence of HPV-16 was 11% in HIV-positive MSM and 9% in MSM. The second most frequent type was HPV-58, with a prevalence of 12% in HIV-positive MSM and 5% in MSM, followed by HPV45 (10% HIV-positive MSM and 6% MSM). The prevalence of oral HPV was lower than that of anal canal HPV (96% HIV-positive MSM, 77% MSM) and external genital site HPV prevalence (61% HIV-positive MSM, 41% MSM). The authors reported that the prevalence of oral HPV in MSM was higher than that in the entire Peruvian population[32].

MSM are more likely to have oral HPV if they have anal HPV infection, and, similarly, more likely to have anal HPV if they have oral HPV[33]. Evidence on anal HPV infection is important for the identification of factors associated with oral HPV. Table 2 shows studies exploring anal HPV infection in MSM in Latin American

cohorts [34-40]. The prevalence of anal HPV ranges from 61% to 100% (Table 2), and the prevalence values are similar to those reported for countries in other regions of the world (92.6%; 95% CI 90.8-94.5%, n = 2718, 1993-2010)[41]. The high prevalence of anal HPV is a sign that should not be ignored in attempts to understand oral HPV in Latin American MSM. Regarding the prevalence of HR-HPV for anal HPV, HPV-16 is the most common type found among the cohorts in Latin America, although the second type of HPV varies among countries (Table 2).

Table 2. Studies investigating the prevalence of anal human papillomavirus in men who have sex with men.

Country	Reference	Group	n/Total	Prevalence of Anal HPV	Prevalence of HR-HPV Genotypes	Prevalence of LR-HPV Genotypes
Argentina	Pando et al[40] 2012	MSM		92.3%	HPV-16: 24.5% HPV-31b: 8.9% HPV-33: 7.2%	HPV 6: 28.6% HPV 11: 21.0% HPV 61: 4.1%
Brazil	Tosato et al[34] 2018	MSM	48/48	100%	HPV-16: 12% HPV-45: 8% HPV-52: 7%	HPV 6: 10% HPV 44: 4% HPV 11: 3%
Cuba	Limia et al[35] 2017	MSM	46/50	92%	Not reported	Not reported
Mexico	Torres-Ibarra et al[36] 2014	MSMHIV+	415/446	93.1%	HPV-16: 21.7% HPV-58: 16.4% HPV-18: 15%	HPV 6: 21.4% HPV 11: 21.1%
Mexico	Mendez-Martínez et al[37] 2014	MSMHIV+	279/324	86.1%	HPV-16: 27.5% HPV-18: 8.6%	Not reported
Mexico	González-Hernández et al[38] 2018	MSMHIV+	54/75	72%	HPV-16: 12.9% HPV-18: 9.2% HPV-59: 9.2%	HPV 6: 22.2% HPV 61: 16.6% HPV 81: 16.6%
Peru	Blas et al[39] 2015	MSMHIV+	96/99	97%	HPV-16: 33.9% HPV-18: 31.7% HPV-52: 24.2%	HPV 6: 37.3% HPV 11:16.7%,

DISCUSSION

Oral HPV and its association with oropharyngeal cancer

The HR-HPV types can persist in the host and are associated with intraepithelial neoplasia and squamous cell cancer in the cervix, vagina, penis, anus, rectum, and oropharynx. HPV-16 is the type most frequently associated with OPC[42].

Head and neck squamous cell carcinoma involve tumors originating from the squamous epithelium of the oral cavity, oropharynx, larynx, and hypopharynx. Head and neck squamous cell carcinoma are divided based on its HPV status: HPV-negative associated with tobacco and alcohol and, HPV-positive associated with HPV infection[43-47]. In the second category, oropharyngeal squamous cell carcinoma is the subtype most frequently associated with HPV[48,49]. Kreimer et al[20] calculated that the worldwide prevalence of oropharyngeal squamous cell carcinoma was 35.6% (95% CI, 32.6-38.7), being higher than the worldwide prevalence of laryngeal SCC (24%, 95% CI 21.8-26.3) and oral SCC (23.5%, 95% CI 21.9-25.1). Recently, Mariz et al[50] calculated an overall pooled prevalence of HPV- oropharyngeal squamous cell carcinoma of 45%. Regarding HPV type status, HPV-16 was the type most associated with oropharyngeal squamous cell carcinoma, and HPV-18 was the second most common type[20,50].

In our review, we found that the prevalence of oral HPV was higher than that found by King et al[19] in a meta-analysis which did not include any study from Latin America: 28.9% (95% CI 19.1-38.7%) in HIV-positive

MSM and 17.1% (95% CI 7.3-26.8%) in MSM. In addition, HR-HPV prevalence was 16.5% (95% CI 8.2-24.8) in HIV-positive MSM and 9.1% (95% CI 4.0-14.2) in MSM[19]. Also, note that the prevalence of oral HPV in MSM in Latin America was higher than that of oncogenic oral HPV found in healthy Latin American men: 1.3% (95% CI 0.5% to 2.7%) and 1.0% (95% CI, 0.4% to 2.2%) in Brazil and Mexico, respectively, with no statistically significant differences between the values ($p = 0.642$)[51].

The studies in MSM in Latin America have found a higher prevalence of HPV in MSM compared with that in heterosexual men; a higher prevalence of HPV in HIV-positive MSM compared with that in MSM; and HPV-16 to be the most common type in HIV-positive MSM or MSM; hence, oral HPV data resemble those from other regions of the world. The evidence should be carefully scrutinized, taking into account the conditions under which the studies were conducted (Table 1). As identification of oral HPV is affected by the assay method used to detect the virus, the variety of methods used among studies makes comparison of the results difficult[19]. Sample collection with a cytobrush or with a punch for tissue seems adequate for specific sites, but the amount of mucosa collected might not be sufficient for use in a detection assay and the number of useful samples may be lower than expected, as occurred in the studies performed by Vianna et al[26] and Anaya-Saavedra et al[28]. Oral rinse sampling has been accepted as a suitable collection technique for oral HPV in epidemiological studies despite its limitations in identifying the specific site of infection[52]. Donà et al[53] obtained 163 oral rinses from MSM to detect HPV and compared the results of those samples with those obtained from oropharyngeal (n = 163) and oral brushing (n = 100) in the same individuals. They reported that the positivity rate in the oral rinse for any HPV type was 58.9% (96/163), while it was 9.9% (95% CI 5.6-16.0) and 8.0 (95% CI 3.4-15.8) for oropharyngeal and oral brushing, respectively[53]. Thus, study limitations should be considered in analyses of the results described here.

Studies have identified risk factors associated with oral HPV for the MSM population. An important risk factor is the large number of oral sex partners in this population. Rollo et al[7] observed that individuals with more than 50 partners presented high oral HPV compared with those with fewer than 50 partners (95% CI 2.49–33.62). Also, Van Aar et al[54] reported that the risk of oral HPV was associated with a higher number of oral sex partners in MSM (95% CI 1.4-4.2 for ≥ 8 compared with ≤ 2 partners). Other risk factors are age, smoking, and the presence of HIV infection[19]. Latin American studies reported risk factors similar to those reported in studies from other regions. Blas et al[32] (Peru) observed that HIV positivity was associated with the high prevalence of oral HPV. Vianna et al[26] (Brazil) noted an association between oral HPV infection and the number of sexual partners (more than 1 partner), while no association was noted with condom use, anal intercourse, the presence of oral lesions, CD4+ count cells, or infection time. Colon et al[27] (Puerto Rico) found that the prevalence of oral HPV increased with age and that detection of oral HPV was higher in men with a higher number of lifetime sex partners (OR = 1.02, 95% CI 1.01-1.03). They also reported that men who had smoked at least once in their lifetime showed three times more oral HPV infection (95% CI 1.15-8.36, OR = 3.10). Castillejos-García et al[29] found an association between smoking and oral HPV, with tobacco smokers presenting a 3.4-fold increased risk of developing oropharyngeal HPV lesions. Anaya-Saavedra et al[28] (Mexico) explored the association between the advance of HIV and HPV oral lesions and found that individuals with oral lesions presented HIV infection at a more advanced stage in comparison with those without HPV oral lesions ($p < 0.023$). Carnalla et al[30] (Mexico) found a higher prevalence of HR-HPV associated with the use of marijuana and sildenafil and/or poppers and also associated with hepatitis B or hepatitis C, gonorrhea, syphilis, chlamydia, and trichomonas. In addition, they reported that the prevalence of HPV-16 and HPV-18 was higher in HIV positive MSM, with a TCD4 count between 200 and 499 cell/mL.

An individual might develop oropharyngeal cancer associated with HPV only if he/she has a preceding HPV infection. Studies have presented promising results on HPV vaccination to prevent oropharyngeal cancer[55], and HPV vaccination is today a beneficial strategy to prevent that type of cancer. There are presently three HPV vaccines: the bivalent Cervarix (GSK, Wavre, Wallonia, Belgium), protecting against infection from HPV16 and 18; the quadrivalent Gardasil (Merck, Rahway, New Jersey, USA), protecting against infection from HPV 6, 11, 16, and 18; and the nonvalent Gardasil 9 (Merck, Rahway, New Jersey, USA), protecting against infection from HPV 6, 11, 16, 18, 31, 35, 45, 52, and 58[55]. Those vaccines have been reported to prevent > 90% of HPV-positive oropharyngeal cancer[55]. In Latin America, the HPV quadrivalent vaccination is widely given to women because cervical cancer associated with HPV is the third most common cancer in the region[56].

Since 2006, the strategy for the administration of the HPV vaccination involves health programs of the WHO, as well as of individual Latin American countries and has been a daunting task[25]. However, a similar strategy for the administration of the HPV vaccination to men has not been performed to date in Latin America. MSM in Latin America are vulnerable and commonly suffer from discrimination[57,58]. Such a reality makes it difficult to approach MSM for HPV vaccine clinical trials; hence, to solve this problem, well-defined ethical

strategies are required to favor the successful participation of MSM[58]. Valuable efforts have been made to explore HPV vaccination in Latin American countries. In Peru, Colon et al[59] surveyed 206 men (32.6% MSM) and found that none had been vaccinated against HPV and that only 28.3% of men knew about the existence of an HPV vaccine. Interestingly, most of those interviewed were willing to be vaccinated. In Mexico, Lazcano-Ponce et al[60] began administering HPV vaccinations in MSM and other susceptible groups as part of a prevention program, and a study is underway to track the efficacy of HPV vaccine in oral HPV. While in other regions a vaccine for men is accepted as part of a HPV prevention program[61], most Latin American countries have delayed adopting similar programs.

Shen et al[62] performed a systematic review to explore the acceptance of HPV vaccine in men. They found that a general men population showed an acceptance rate of 47.04% (95% CI: 39.23%-54.93%) and men with a sexual orientation showed an acceptance rate of 62.23% (95% CI: 52.93%-71.10%). The systematic review included 57 studies from four continents, none of which were from the Latin American region. Education and publicity regarding the HPV vaccine is important to promote its use among men as are education about the HPV vaccine and about HPV as a sexually transmitted infection (STI) early in life[62]. Knowledge of some STIs might be distinct from other STIs among young people. For instance, high-school and university students do not recognize HPV as different from other STIs[63]. Also, in the young, while the use of a condom is recognized as a method of preventing an STI, it is more identified as a method of preventing pregnancy; young people might not use a condom in sexual intercourse if they are not concerned with the risk of pregnancy[63,64]. HPV vaccine uptake in young people is also of great importance in the prevention of the infection, but knowledge of the vaccine and its use varies among young people from different countries[65]. Latin American countries should adopt educational strategies to prevent the infection in young people, and public health authorities should promote preventive programs on HPV infection for the whole population, with special emphasis on teenagers, high-school students, and university students.

CONCLUSIONS

Studies in Latin America have shown the significant presence of oral HPV in MSM groups. As evidenced by studies, oral HPV appears as a common coinfection in MSM, and HR-HPV genotypes, among which HPV-16 is the most common, have been well identified in that population. Indeed, Latin America faces an important challenge regarding oral HPV. The evidence supports the need for the development of preventive actions to reduce oral HPV and HIV/HPV coinfection and, consequently, to avoid oropharyngeal cancer. Public health policies specific to MSM should be urgently developed and directed to that vulnerable population. However, few studies regarding oral HPV in MSM in Latin America offer strong evidence to support the design and application of preventive programs. Thus, promotion and the development of investigations on this topic are imperative for a better understanding of oral HPV in MSM.

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ORCID ID:
Mario RB Guapillo-Vargas: 0003-3935-3332
Jaime Jaramillo Vázquez: 0000-0003-4465-8720
Bernardino I. Cerda Cristerna: 0000-0003-1022-1387

CONFLICT OF INTERESTS:
Authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT:
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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