Prevalence and incidence of anal human papillomavirus infection in Mexican men: Need for universal prevention policies

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Abstract

Objective. Describe the natural history of anal HPV among men. **Materials and methods.** Prospective study among men 18-70 years (n=665), from Cuernavaca, Mexico who completed questionnaires and provided specimens (HPV genotyped) at enrollment and 1+ follow-up visit. HPV prevalence and incidence were estimated. Prevalence ratios were calculated with Poisson regression using robust variance estimation. Person-time for incident HPV infection was estimated using number of events modeled as Poisson variable for total person-months. **Results.** Anal infection prevalence: any HPV type=15%, high-risk=8.4%, HPV16=1.4%, tetravalent vaccine types (4vHPV)=4.4%, nonavalent vaccine types (9vHPV)=6.3%. Factors associated with prevalence: 50+ lifetime female sex partners (adjusted prevalence ratio, a PR=3.25, 95% CI:1.12-9.47), 10+ lifetime male sex partners (aPR=3.06, 95%CI:1.4-6.68), and 1+ recent male anal sex partners (aPR=2.28, 95%CI:1.15-4.5). Anal incidence rate: high-risk HPV=7.8/1000

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Resumen

Objetivo. Generar evidencia que apoye la vacunación universal contra VPH. **Material y métodos.** Estudio prospectivo con hombres 18-70 años (n=665) de Cuernavaca, México con cuestionarios y genotipificación de VPH en muestras (2+mediciones). Se estimó prevalencia e incidencia; se calcularon tasas de prevalencia con regresión Poisson. Se estimó persona-tiempo para infecciones incidentes. **Resultados.** Prevalencia de infección anal: cualquier tipo de VPH=15%, alto-riesgo=8.4%, VPH16=1.4%, tipos en vacuna tetravalente=4.4% y tipos en vacuna nonavalente=6.3%. Factores asociados con infección prevalente: 50+ parejas sexuales femeninas en la vida (tasa de prevalencia ajustada, TPa=3.25, IC95%:1.12-9.47); 10+ parejas sexuales masculinas en la vida (TPa=3.06, IC95%:1.4-6.68) y 1+ parejas masculinas (sexo anal) recientes (TPa=2.28, IC95%:1.15-4.5). Tasas de incidencia para infección anal: VPH alto-riesgo=7.8/1000 persona-meses (IC95%:6.0-10.1), VPH 16=1.8/1000 persona-meses (95%IC:1.1-2.9), tipos en vacu-

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person-months (95%CI:6.0-10.1), HPV16=1.8/1000 person-months (95%CI:1.1-2.9),4vHPV=3.4/1000 person-months (95%CI:2.3-4.9) and 9vHPV=5.5/1000 person-months (95%CI:4.1-7.5). **Conclusions.** Implementation of universal HPV vaccination programs, including men, is a public health priority.

Keywords: human papilloma virus; prevalence; incidence; anal canal; men; apillomavirus vaccines

na tetravalente=3.4/1000 persona-meses y tipos en vacuna nonavalente=5.5/1000 persona-meses. **Conclusiones.** Implementación de programas de vacunación universal (incluyendo hombres) contra VPH es una prioridad en salud pública.

Palabras clave: virus del papiloma humano; prevalencia; incidencia; canal anal; hombres; vacunación universal contra VPH

In men, human papillomavirus (HPV) infections are associated with genital warts and intraepithelial neoplasm, predominantly in the anal canal.[1] Quantification of HPV prevalence and incidence in the anal canal has been described for heterosexual men,[2] men who have sex with men (MSM),[3] bisexual men[4] and transpeople[5] as well as in men with HIV[6] and immunosurpressed people.[7] In many of these population groups, the frequency of high- and low-risk HPV is extremely high; this can lead not only to a greater likelihood of transmitting HPV to their sexual partners[8] but also to increased risk of anal intraepithelial neoplasm.[9]

Sexual behaviors are the main determinants of incident HPV infections; also, the HIV population is more likely to have a persistent infection in the anal canal; the largest burden of HPV related diseases is found in people with HIV.[10] In addition, heterosexual men with genital HPV infections are at greater risk of infection in the anal canal; autoinoculation is, hypothetically, a mechanism which could explain this last association.[3] Studies indicate that frequency of HPV in the anal canal is associated with increased incidence and mortality due to anal cancer in higher-income countries. For example, in 2008-2012 in the United States there was an annual average of 1 600 cases of anal cancer in men attributable to HPV.[11] Likewise, since people with HIV are living longer due to anti-retroviral treatments, their risk for developing HPV-related lesions, and consequently cancer in the ano-genital region, has multiplied.[12]

Given the above, recently some parts of the world have implemented public policies on population-level vaccination against HPV that include coverage of men.[13] The desired impact of these policies can be framed from a number of perspectives: gender equity,[14] increased universal coverage,[15] or protection of people who are at greater risk of HPV and associated negative outcomes.[16] This article describes findings on the prevalence and incidence of infections in the anal canal with specific HPV types among Mexican men who participated in an international research initiative known as the HIM study.[17,18]

Materials and methods

Study population and design

The HIM Study provides prospective data on the evolution of HPV infection in men. Within this study, 4 074 men aged 18-70 years were recruited in three countries; a total of 1 330 participants were included in Mexico.[17,18] A detailed description of the general HIM study has been published previously.[17-19] In Mexico, participants were recruited in the city of Cuernavaca located in the central state of Morelos. The informed consent of all the participants was obtained. For this analysis, 665 men were included who had at least two study visits for sample collection from the anal canal between November 2005 and December 2010. The ethics, biosecurity and research committees of the *Instituto Nacional de Salud Pública* and the *Instituto Mexicano del Seguro Social* (IMSS) approved the research protocol. Men who had an existing penile or anal cancer diagnosis, symptoms or previous treatment of a sexually transmitted infection, or a history of genital or anal warts, and HIV-positive individuals were excluded from the study. Men from different population groups were recruited, including university students, healthcare users, and members of organized healthcare systems (particularly the IMSS).

Study procedures

During all follow-up visits, participants completed a computer-assisted self-interview (CASI) questionnaire designed to collect data on social and behavioral variables related to HPV infection, including condom use, lifetime male and female sex partners, new sex partners, and tobacco and alcohol use.[3] In addition, a

physical exam was carried out, and samples were collected for laboratory analysis for HPV diagnosis; up to 10 clinical visits, scheduled every 6 months during a 4-year follow-up period, were conducted. Urine, blood, anogenital epithelium and oral samples were collected. Separate saline-wetted Dacron swabs were used to collect exfoliated skin cells from the penis (i.e., coronal sulcus, glans, and ventral and dorsal areas of shaft) and scrotum. Then, using a separate swab, 360° of the anal epithelium was swabbed between the anal os and the anal canal dentate line. Gloves were changed after each sample was collected, and each swab was placed into a separate vial with standard transport medium and stored at –80°C until processing at the lab in Tampa, Florida. [20] All personnel were trained in sample collection, emphasizing the importance of avoiding touching the perianal skin with the swab.

HPV Detection

Samples were analyzed for HPV DNA as described above.[18] Briefly, DNA was extracted using the QIAamp Media MDx kit (Qiagen). The polymerase chain reaction (PCR) consensus primer system (PGMY 09/11) was used to amplify a fragment of the HPV L1 gene.[21] HPV genotyping was conducted on all samples using DNA probes labeled with biotin in order to detect 37 HPV types: 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51–56, 58, 59, 61, 62, 64, 66–73, 81–84, IS39, and CP6108.[22] Accuracy and potential contamination were assessed using non-template negative controls and CaSki DNA–positive controls.[20]

Statistical analysis

Prevalence and incidence were estimated for any HPV type –whether high-risk (HR-HPV: 16/18/31/33/35/39/45/51/52/56/58/59/68) or low-risk (LR-HPV: 6/11/26/40/42/53/54/55/61/62/64/66/67/69/70/71/72/73/81/82/IS39/83/84/89)–, for the four types (6/11/16/18) included in the tetravalent HPV vaccine (4vHPV), for the nine types (6/11/16/18/31/33/45/52/58) included in the nonavalent HPV vaccine (9vHPV), and for each specific HPV type. The classification of any HPV infection was defined as a positive test result for at least one of 37 HPV genotypes. HPV infections with single or multiple high-risk virus types were classified as high-risk.[23]

In order to assess factors associated with prevalent HPV infection, prevalence ratios (PRs) and 95%CI were calculated with Poisson regression using robust variance estimation. Age was forced into the multivariable model, while other factors that remained in the final model were $p<0.05$.

Person-time for newly acquired HPV infection was estimated by use of time from study entry to the date of the first detection of HPV DNA, assuming a new infection arose at the date of detection. The calculation of the exact 95%CI for incidence estimates was based on the number of events modeled as a Poisson variable for the total person-months.

Results

Anal HPV infections (with any HPV type) were detected at baseline in 100 out of the 665 Mexican men included in this analysis; i.e. the prevalence of these infections was 15% (table I). Prevalence of HPV infection in the anal canal was 8.4% for high-risk (oncogenic) HPV types, and 10.7% for low-risk (non-oncogenic) types. Among the specific HPV types with the highest prevalence in the anal canal were HPV-16 (1.4%) and HPV-6 (2.3%). The HIM Study found in Mexican men a prevalence of 4.4% of infection in the anal canal with one or more of the HPV types included in the tetravalent HPV vaccine, and of 6.3% of infection with one or more of the HPV types included in the nonavalent vaccine.

There were statistically significant differences between men with and without a prevalent HPV infection in the anal canal, in terms of age ($p=0.03$), marital status ($p=0.01$), sexual orientation ($p<0.0001$) and lifetime number of male partners ($p<0.0001$) (table II). No differences between men with and without a prevalent HPV infection were observed for the other characteristics.

Among Mexican men in the HIM Study, the factors associated with prevalent infection with any HPV type in the anal canal were: having had more than 50 female sex partners in their lifetime, compared with 1 or fewer lifetime female sexual partners (adjusted prevalence ratio, aPR=3.25, 95%CI 1.12-9.47); having had 1-9 male anal sex partners in their lifetime (aPR=1.84, 95%CI 1.07-3.17) or 10 or more male anal sex partners in their lifetime (aPR=3.06, 95%CI 1.4-6.68), both compared to no male sexual partners, and having had one or more recent male anal sex partners, compared to no recent male sexual partners (aPR=2.28, 95%CI 1.15-4.5) (table II).

Statistically significant differences between men with and without an incident HPV infection (of any type acquired after baseline) in the anal canal were observed for marital status ($p<0.0001$), sexual orientation ($p<0.0001$) and lifetime number of male sex partners ($p<0.0001$) (table III).

The incidence rate for anal infection with any type of HPV was 11.0/1 000 person-months (95%CI 8.7-14.0),

Table I
Type distribution of prevalent anal HPV infections overall and by specific type in Mexican men in the HIM study. Cuernavaca, Morelos, 2005-2010

HPV type	Prevalent HPV infection N (%)
Any HPV type	100 (15.0)
High risk (HR)	56 (8.4)
16	9 (1.4)
18	3 (0.5)
31	1 (0.2)
33	4 (0.6)
35	2 (0.3)
39	8 (1.2)
45	4 (0.6)
51	12 (1.8)
52	5 (0.8)
56	7 (1.1)
58	5 (0.8)
59	10 (1.5)
68	6 (0.9)
Low risk (LR)	71 (10.7)
6	15 (2.3)
11	4 (0.6)
26	0 (0)
40	1 (0.2)
42	2 (0.3)
53	6 (0.9)
54	7 (1.1)
55	3 (0.5)
61	10 (1.5)
62	5 (0.8)
64	5 (0.8)
66	7 (1.1)
67	0 (0)
69	0 (0)
70	3 (0.5)
71	6 (0.9)
72	2 (0.3)
73	3 (0.5)
81	9 (1.4)
82	1 (0.2)
83	3 (0.5)
84	14 (2.1)
89	12 (1.8)
139	1 (0.2)
4vHPV*	29 (4.4)
9vHPV‡	42 (6.3)

Percentages do not equal 100 because men could have more than one HPV type; in addition, the Linear Array analysis identifies 37 HPV types, and therefore some types are considered "not classifiable"

* 4vHPV: one or more of the 4-valent HPV vaccine types (6, 11, 16, 18)
‡ 9vHPV: one or more of the 9-valent HPV vaccine types (6, 11, 16, 18, 31, 33, 45, 52, 58)

HPV: human papillomavirus

while the incidence rate for anal infection for high-risk HPV types was 7.8/1000 person-months (95%CI 6.0-10.1), and 8.4/1 000 person-months (95%CI 6.5-10.9) for low-risk HPV types (table IV). The incidence rate specifically for one or more of the HPV types included in the tetravalent HPV vaccine was 3.4/1 000 person-months (95%CI 2.3-4.9), and 5.5/1 000 person-months (95%CI 4.1-7.5) for one or more of the HPV types included in the nonavalent vaccine.

Discussion

Prevalence of HPV infections in the anal canal among Mexican men was 15%. The rate at which new (incident) infections were acquired was 11 new infections per 1 000 person-months. Among Mexican men, the factors associated with prevalent HPV infection in the anal canal were related to sexual behavior, above all to having multiple sexual partners, especially male anal sex partners.

Before the HIM Study cohort was developed to describe the natural history of HPV infection in men, the existing publications on epidemiological studies established hypotheses about the factors associated with HPV infection in the ano-genital region in men. Based on cross-sectional studies and on the initial stages of cohort studies, the scientific community knew that HPV infections in the anal canal in men were closely associated to certain sexual behaviors,[24] such as having multiple sexual partners,[25] and also to the frequency with which men had contact with new sexual partners.[26] Furthermore, the strongest associations were for having anal sex with other men, as well as for existing sexually transmitted infections.[24,26,27] Consequently, HPV infection contributes significantly to the burden of disease among men. However, currently no population-based screening methods for detecting HPV-related disease in men have been validated.

Ten years after the introduction of HPV vaccines, there is evidence regarding the main population-level effects in terms of effectiveness. One of the observed impacts is that incident HPV 6/11/16/18 infections have decreased by up to 90% in populations with over 65% coverage with HPV vaccination in women.[28] Likewise, a decrease of close to 90% in genital warts has been estimated, with a reduction of low-grade cytological abnormalities by nearly 45%, and of high-grade histological lesions by up to 85%.[28]

In terms of the population-level impact, a herd effect in men has been documented after the introduction of HPV vaccination in women. Heterosexual men residing in contexts with above 50% coverage of HPV vaccination in women show a significant reduction of HPV infections and of ano-genital lesions produced

Table II

Baseline comparison by demographic characteristics and factors associated with prevalent infection in the anal canal (with any HPV type) among Mexican men in the HIM Study. Cuernavaca, Morelos, 2005-2010

	*Mexico (n=665)**			*Mexico (n=665*)*	
	No Infection	*Infection*	*P Value‡*	*uPR*	*aPR*
Age			0.03		
18-30	219(80.8)	52(19.2)		1.00 (ref)	1.00 (ref)
31-44	262(86.8)	40(13.2)		0.69(0.47-1.01)	0.69(0.47-1.01)
45-70	84(91.3)	8(8.7)		0.45(0.22-0.92)	0.54(0.26-1.12)
Years of education			0.24		
≤12 Years	328(83.5)	65(16.5)		1.00 (ref)	1.00 (ref)
13-15 Years	59(89.4)	7(10.6)		0.64(0.31-1.34)	0.57(0.29-1.14)
≥16 Years	177(87.6)	25(12.4)		0.75(0.49-1.15)	0.72(0.48-1.09)
Missing	1(25.0)	3(75.0)			
Marital status			0.01		
Single	130(79.3)	34(20.7)		1.00 (ref)	
Married/cohabiting	410(87.6)	58(12.4)		0.6(0.41-0.88)	
Divorced/separated/widowed	23(74.2)	8(25.8)		1.24(0.64-2.43)	
Missing	2(100.0)	0(0.0)			
Smoking status			0.12		
Never	256(84.2)	48(15.8)		1.00 (ref)	
Current	174(82.5)	37(17.5)		1.11(0.75-1.64)	
Former	135(90.0)	15(10.0)		0.63(0.37-1.09)	
Monthly alcohol intake			0.7		
0 drinks	117(86.7)	18(13.3)		1.00 (ref)	
1 - 30 drinks	312(85.0)	55(15.0)		1.12(0.69-1.84)	
31+ drinks	112(83.0)	23(17.0)		1.28(0.72-2.26)	
Missing	24(85.7)	4(14.3)			
Circumcised			0.47		
Yes	98(87.5)	14(12.5)		1.00 (ref)	
No	467(84.4)	86(15.6)		1.24(0.73-2.11)	
Lifetime # of female sex partners			0.21		
0-1	88(84.6)	16(15.4)		1.00 (ref)	1.00 (ref)
2-9	311(86.1)	50(13.9)		0.9(0.54-1.51)	1.25(0.76-2.04)
10-49	130(82.8)	27(17.2)		1.12(0.63-1.97)	1.75(0.98-3.13)
50+	7(63.6)	4(36.4)		2.36(0.96-5.83)	3.25(1.12-9.47)
Refused	29(90.6)	3(9.4)		0.61(0.19-1.96)	0.74(0.18-3.07)
Lifetime # of male anal sex partners			<.0001		
0	513(87.7)	72(12.3)		1.00 (ref)	1.00 (ref)
1-9	43(69.4)	19(30.6)		2.49(1.62-3.84)	1.84(1.07-3.17)
10+	4(33.3)	8(66.7)		5.42(3.44-8.54)	3.06(1.4-6.68)
Missing	5(83.3)	1(16.7)			
Recent # of female sex partners					
None				1.00 (ref)	
1				0.65(0.42-1.01)	
2				0.99(0.58-1.72)	
3+				1.01(0.49-2.08)	
Refused				0.96(0.44-2.09)	
Recent # of male anal sex partners					
None				1.00 (ref)	1.00 (ref)
1+				4.68(3.25-6.73)	2.28(1.15-4.5)
Sexual orientation			<.0001		
MSW	447(88.0)	61(12.0)		1.00 (ref)	
MSM	9(56.3)	7(43.8)		3.64(1.99-6.66)	
MSMW	46(64.8)	25(35.2)		2.93(1.98-4.35)	
Never had sex	34(89.5)	4(10.5)		0.88(0.34-2.28)	
Missing	29(90.6)	3(9.4)			

Abbreviations: MSW: men who have sex only with women; MSM: men who have sex only with men; MSMW: men who have sex with men and women; Never had sex: reported no sexual contact with males or females; uPR= unadjusted prevalence ratios; aPR= adjusted prevalence ratios

* The total sample of Mexican men in the HIM study is 1 330 participants; the sample for this analysis consisted of 665 Mexican men who had at least two study visits

‡ *P* values were calculated using Monte Carlo estimation of exact Pearson chi-square tests to compare characteristics of men with and without HPV. Missing values were not included in *p* value calculations

Prevalence ratios (PRs) and 95% CI were calculated with Poisson regression, using robust variance estimation. Age was forced into the multivariable model, and factors that remained in the final model were $p<0.05$

Table III

Demographic characteristics of Mexican HIM Study participants, comparing men with and without an incident HPV infection in the anal canal during follow-up. Cuernavaca, Morelos, 2005-2010

	Mexico (n=665)		
	No infection	Infection	P Value*
Age			0.21
18-30	230(84.9)	41(15.1)	
31-44	267(88.4)	35(11.6)	
45-70	84(91.3)	8(8.7)	
Years of education			0.94
≤12 years	344(87.5)	49(12.5)	
13-15 years	58(87.9)	8(12.1)	
≥16 years	175(86.6)	27(13.4)	
Missing	4(100.0)	0(0.0)	
Marital status			<.0001
Single	125(76.2)	39(23.8)	
Married/cohabiting	426(91.0)	42(9.0)	
Divorced/separated/widowed	28(90.3)	3(9.7)	
Missing	2(100.0)	0(0.0)	
Current smoker			0.18
Current	177(83.9)	34(16.1)	
Former	134(89.3)	16(10.7)	
Never	270(88.8)	34(11.2)	
Missing			
Monthly alcohol			0.17
0 drinks	122(90.4)	13(9.6)	
1 - 30 drinks	322(87.7)	45(12.3)	
31+ drinks	112(83.0)	23(17.0)	
Missing	25(89.3)	3(10.7)	
Sexual orientation			<.0001
MSW	465(91.5)	43(8.5)	
MSM	4(25.0)	12(75.0)	
MSMW	51(71.8)	20(28.2)	
Never had sex	34(89.5)	4(10.5)	
Missing	27(84.4)	5(15.6)	
Circumcised			0.76
No	482(87.2)	71(12.8)	
Yes	99(88.4)	13(11.6)	
Lifetime # of female sex partners			0.18
0-1	85(81.7)	19(18.3)	
2-9	324(89.8)	37(10.2)	
10-49	137(87.3)	20(12.7)	
50+	9(81.8)	2(18.2)	
Refused	26(81.3)	6(18.8)	
Lifetime # of male anal sex partners			<.0001
0	533(91.1)	52(8.9)	
1-9	42(67.7)	20(32.3)	
10+	2(16.7)	10(83.3)	
Missing	4(66.7)	2(33.3)	

Abbreviations: MSW: men who have sex only with women; MSM: men who have sex only with men; MSMW: men who have sex with men and women; Never had sex: reported no sexual contact with males or females

* *P* values were calculated using Monte Carlo estimation of exact Pearson chi-square tests comparing characteristics of men with and without HPV within each country. Missing values were not included in *p* value calculations

Table IV

Person-months to incident HPV infection and HPV incidence rates in the anal canal among Mexican men in the HIM study. Cuernavaca, Morelos, 2005-2010

HPV type	Incident HPV infection	
	Number/ person-months*	IR (95%CI)‡
Any HPV type	67/6076	11.0(8.7-14.0)
High risk (HR)	58/7461	7.8(6.0-10.1)
16	15/8447	1.8(1.1-2.9)
18	7/8675	0.8(0.4-1.7)
31	3/8793	0.3(0.1-1.1)
33	4/8611	0.5(0.2-1.2)
35	2/8761	0.2(0.1-0.9)
39	4/8532	0.5(0.2-1.2)
45	10/8639	1.2(0.6-2.2)
51	12/8362	1.4(0.8-2.5)
52	11/8528	1.3(0.7-2.3)
56	3/8605	0.4(0.1-1.1)
58	4/8628	0.5(0.2-1.2)
59	15/8499	1.8(1.1-2.9)
68	6/8494	0.7(0.3-1.6)
Low risk (LR)	57/6774	8.4(6.5-10.9)
6	7/8318	0.8(0.4-1.8)
11	4/8667	0.5(0.2-1.2)
26	1/8821	0.1(0.0-0.8)
40	4/8762	0.5(0.2-1.2)
42	5/8678	0.6(0.2-1.4)
53	12/8502	1.4(0.8-2.5)
54	8/8553	0.9(0.5-1.9)
55	5/8683	0.6(0.2-1.4)
61	8/8404	1.0(0.5-1.9)
62	11/8535	1.3(0.7-2.3)
64	0/8828	0.0(0.0-0.0)
66	5/8455	0.6(0.2-1.4)
67	1/8828	0.1(0.0-0.8)
69	1/8822	0.1(0.0-0.8)
70	5/8711	0.6(0.2-1.4)
71	2/8623	0.2(0.1-0.9)
72	3/8730	0.3(0.1-1.1)
73	1/8754	0.1(0.0-0.8)
81	3/8577	0.4(0.1-1.1)
82s§	2/8724§	0.2(0.1-0.9)§
83	2/8777	0.2(0.1-0.9)
84	2/8776	0.2(0.1-0.9)
89	12/8231	1.5(0.8-2.6)
139	16/8438	1.9(1.2-3.1)
4vHPV#	27/7997	3.4(2.3-4.9)
9vHPV&	42/7598	5.5(4.1-7.5)

* number/person months: number of men with infection/person-months
‡ IR= Incidence rates per 1000 person-months
§ HPV 82 subtype IS39
\# 4vHPV: one or more of the 4-valent HPV vaccine types (6, 11, 16, 18)
& 9vHPV: one or more of the 9-valent HPV vaccine types (6, 11, 16, 18, 31, 33, 45, 52, 58)

by these infections.[29] This has been observed in men up to age 40 years. However, the optimum protection at population-level that can be obtained through HPV vaccination has not yet been attained, for lesions caused by HPV infection continue to be a significant cause of morbidity and mortality worldwide.[30] This situation implies that the implementation of universal HPV vaccination programs with a high level of population coverage and the inclusion of men in the near future are public health priorities. Also needed are innovative approaches to cervical cancer prevention and control, such as combined screening and vaccination strategies among adult women[31] as well as the targeting of population groups with the highest incidence of, and mortality due to cervical and other cancers (including anal cancer), and evaluations of the cost-effectiveness of HPV vaccination among adult men.[12]

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