Research Article

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# Comparison of the Natural History of Genital HPV Infection among Men by Country: Brazil, Mexico, and the United States

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## Abstract

**Background:** Male genital human papillomavirus (HPV) prevalence and incidence has been reported to vary by geographical location. Our objective was to assess the natural history of genital HPV by country among men with a median of 48 months of follow-up.

**Methods:** Men ages 18–70 years were recruited from United States ($n = 1{,}326$), Mexico ($n = 1{,}349$), and Brazil ($n = 1{,}410$). Genital specimens were collected every 6 months and HPV genotyping identified 37 HPV genotypes. Prevalence of HPV was compared between the three countries using the Fisher exact test. Incidence rates and 95% confidence intervals were calculated. The median time to HPV clearance among men with an incident infection was estimated using the Kaplan–Meier method.

**Results:** The prevalence and incidence of the genital HPV types known to cause disease in males (HPV 16 and 6) was significantly higher among men from Brazil than men from Mexico. Prevalence and incidence of those genital HPV types in the United States varied between being comparable with those of Mexico or Brazil. Although genital HPV16 duration was significantly longer in Brazil ($P = 0.04$) compared with Mexico and the United States, HPV6 duration was shortest in Brazil ($P = 0.03$) compared with Mexico and the United States.

**Conclusions:** Men in Brazil and Mexico often have similar, if not higher prevalence of HPV compared with men from the United States.

**Impact:** Currently, there is no routine screening for genital HPV among males and while HPV is common in men, and most naturally clear the infection, a proportion of men do develop HPV-related diseases. Men may benefit from gender-neutral vaccine policies. *Cancer Epidemiol Biomarkers Prev; 26(7); 1043–52. ©2017 AACR.*



## Introduction

Infectious agents can interact with human hosts in a multitude of ways, and their ability to cause cancer is a major public health concern. Infectious agents caused 16% of the 12.7 million new cancer cases worldwide in 2008 (1). Four major agents are responsible for 80% of these infection-related cancers: hepatitis B virus, hepatitis C virus, *Helicobacter pylori*, and human papillomavirus (HPV). HPV causes several types of cancers and genital warts in both males and females (2) and HPV can be transmitted through sexual contact and potentially through autoinoculation (3).

At the male genitals, HPV causes two types of external genital lesions: genital warts and penile cancer. The HPV genotypes that are most frequently detected in genital warts are HPV6 and 11 (96%–100%; refs. 2, 4) and HPV 16 is the predominant type detected in penile cancer (5–11). Genital warts have a high likelihood of reoccurrence and multiple treatments can be costly (12). Although penile cancer is considered a rare cancer with 22,000 estimated cases per year worldwide, it is associated with high morbidity and mortality (1).

Male genital HPV prevalence and incidence has been reported to vary by geographical location (13–15). Geographical differences in HPV prevalence may explain the differences in HPV-related cancer incidence worldwide. We previously have described the prevalence, incidence, and duration ($n = 1{,}159$) of genital HPV by country among men from Brazil, Mexico, and the United States that were the first to enroll into the HPV Infection in Men (HIM) Study (16, 17). Here, we expand our analyses to the complete cohort of 4,085 men with a median of 48 months of follow-up and describe the natural history of genital HPV by country, needed to inform vaccine policy discussion in each country.

## Materials and Methods

### Study population

The HIM Study enrolled 4,123 men ages 18–70 years living in Tampa, FL; Cuernavaca, Mexico; and Sao Paulo, Brazil, between July 2005 and June 2009. A full description of the study

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procedures has been published (16, 17). Participants returned for study visits every 6 months and were given a physical exam where multiple specimens were obtained for laboratory analysis. Men who had two or more study visits were included in this analysis ($n = 4,085$). Among these 4,085 men, 1,410 were from Brazil, 1,349 from Mexico, and 1,326 from United States.

All participants provided written informed consent. Study protocols were approved by the Institutional Review Boards at the University of South Florida (Tampa, FL), the Ludwig Institute for Cancer Research, the Centro de Referencia e Treinamento em Doencas Sexualmente Transmissiveis e AIDS (Sao Paulo, Brazil), and the Instituto Nacional de Salud Publica (Cuernavaca, Mexico).

***Genital skin specimen collection for HPV detection.*** Participants underwent a clinical examination at each visit. Using prewetted Dacron swabs, genital specimens were collected from the coronal sulcus/glans penis, penile shaft, and scrotum (17). These specimens were combined into one sample per participant and archived. Specimens underwent DNA extraction (Qiagen Media Kit), PCR analysis, and HPV genotyping (Roche Linear Array; ref. 18). If samples tested positive for β-globin or an HPV genotype, they were considered adequate and were included in the analysis. The linear array assay tests for 37 HPV types, classified as high risk (HR-HPV; types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) or low risk (LR-HPV; types 6, 11, 26, 40, 42, 53, 54, 55, 61, 62, 64, 66, 67, 69, 70, 71, 72, 73, 81, 82, 82 subtype IS39, 83, 84, and 89; ref. 19). The HPV genotypes were further classified as the HPV types detected within the 4vHPV vaccine (6/11/16/18) and the 9vHPV vaccine (6/11/16/18/31/33/45/52/58). Non-4vHRHPV are the other high risk (HR-HPV) HPV genotypes that are not covered by the 4vHPV vaccine (31/33/35/39/45/51/52/56/58/59/68), and non-9vHRHPV are the other HR-HPV genotypes that are not covered by the 9vHPV vaccine (35/39/51/56/59/68).

### Statistical analysis

In the HIM Study, sexual orientation was purposefully not asked to decrease risk of reporting bias of sexual behavior. Instead, detailed information regarding sexual behavior was assessed and sex is defined as oral, vaginal, or anal sex. Using responses to these questions at baseline, we defined MSM as ever having sex with a man, MSMW as having sex with both men and women, MSW only have sex with women, and virgins are those that reported no sex with men or women.

***Prevalence.*** Differences in demographic and sexual behavior characteristics between men who did or did not have a prevalent HPV infection (any HPV type) at baseline were calculated within each country using Monte Carlo estimation of the exact Pearson $\chi^2$ test (Table 1). We also calculated differences in demographic and sexual behavior characteristics between men who did or did not have a prevalent HPV infection (any HPV type) at baseline across the three countries (global $P$ value) using the Wald $\chi^2$ test. Prevalence of each HPV genotype was compared between the three countries using the Fisher exact test. To assess factors associated with prevalent HPV infection within each country, prevalence ratios (PR) and 95% confidence intervals (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 retained at $P < 0.05$.

***Incidence and clearance.*** Differences in baseline demographic and sexual behavior characteristics between men with and without an incident HPV infection (any HPV type) were calculated within each country using Monte Carlo estimation of the exact Pearson $\chi^2$ test. We also calculated differences in baseline characteristics between men with and without an incident HPV infection across the three countries (global $P$ value) using the Wald $\chi^2$ test.

Person time for newly acquired HPV infection was estimated by use of the time from study entry to the date of the first detection of HPV DNA, assuming a new infection arose at the date of detection. For individual and grouped HPV incidence analyses, only the first acquired infection was considered for a given HPV type or group. Incidence analyses included only men who tested negative for a given individual HPV type or grouped HPV infection category at baseline, so, for example, men with any HPV type prevalent at enrollment were not included in the grouped "any HPV" incidence. The calculation of the exact 95% CIs for incidence estimates was based on the number of events modeled as a Poisson variable for the total person-months. Incidence rate ratios (IRR) and 95% CIs were also calculated on the basis of Poisson assumption comparing incidence rates between countries.

HPV clearance was defined as two consecutive negative test results following a positive test, excluding infections detected for the first time at a participant's final visit and prevalent infections. For grouped HPV clearance analyses, we adjusted for within-subject correlation, as men may have been infected with multiple HPV types within a defined group (e.g., positive for both HPV 16 and 18, which are both considered high risk). The median time to HPV clearance (median duration) among men with an incident infection was estimated using the Kaplan Meier (KM) method for individual HPV infections, with the clustered KM method used for grouped HPV infections (20). To model the association between country and clearance, we employed Cox proportional hazards regression with and without the robust covariance matrix estimator for grouped and individual HPV clearance, respectively (21).

## Results

### Prevalence

The overall HPV (any type) prevalence among 4,085 men participating in the HIM Study was 52.3%. Overall HPV (any type) prevalence did significantly differ ($P < 0.001$) by country with Brazil (60.2%) having the highest prevalence compared with Mexico (49.2%) and the United States (46.9%; Table 2). In Brazil, HPV prevalence was associated with age ($P = 0.01$), marital status ($P = 0.0002$), and number of lifetime female sexual partners ($P < 0.0001$; Table 1). HPV prevalence in Mexico was not associated with age ($P = 0.87$) but was associated with number of lifetime female sexual partners ($P < 0.0001$). In the United States, HPV prevalence was associated with age ($P < 0.0001$), smoking status ($P < 0.0001$), and number of lifetime female sexual partners ($P < 0.0001$). When comparing demographic and sexual characteristics across the three countries, marital status ($P < 0.0001$), smoking status ($P < 0.0001$), and total number of female sexual partners ($P < 0.0001$) were differentially associated with HPV prevalence (Table 1, global $P$ value).

HPV genotype prevalence by country is described in Table 2. Prevalence of several HPV types significantly differed by country. HPV16 prevalence was highest among men from Brazil (9.2%) compared with men from Mexico (5.6%) and the United States (8.4%). HPV6 prevalence, which causes genital warts, was

**Table 1.** Demographic characteristics for 4085 men at HIM Study baseline comparing men with and without any prevalent HPV infection by country

| | Brazil ($n = 1410$) | | | Mexico ($n = 1349$) | | | United States ($n = 1326$) | | | Global |
|---|---|---|---|---|---|---|---|---|---|---|
| | No infection | Infection | $P^a$ | No infection | Infection | $P^a$ | No infection | Infection | $P^a$ | $P^b$ |
| Age | | | 0.01 | | | 0.87 | | | <.0001 | 0.11 |
| 18–30 | 207 (37.2) | 350 (62.8) | | 284 (50.9) | 274 (49.1) | | 508 (58.3) | 364 (41.7) | | |
| 31–44 | 266 (39.4) | 409 (60.6) | | 315 (51.2) | 300 (48.8) | | 121 (43.1) | 160 (56.9) | | |
| 45–74 | 88 (49.4) | 90 (50.6) | | 86 (48.9) | 90 (51.1) | | 75 (43.4) | 98 (56.6) | | |
| Race | | | 0.55 | | | 0.73 | | | <.0001 | <.0001 |
| White | 331 (38.4) | 531 (61.6) | | 33 (45.8) | 39 (54.2) | | 459 (51.9) | 425 (48.1) | | |
| Black | 174 (43.0) | 231 (57.0) | | 1 (33.3) | 2 (66.7) | | 99 (43.4) | 129 (56.6) | | |
| Asian/PI | 8 (36.4) | 14 (63.6) | | 0 (0.0) | 0 (0.0) | | 75 (83.3) | 15 (16.7) | | |
| Other | 29 (37.2) | 49 (62.8) | | 620 (51.0) | 595 (49.0) | | 24 (58.5) | 17 (41.5) | | |
| Refused | 19 (44.2) | 24 (55.8) | | 31 (52.5) | 28 (47.5) | | 47 (56.6) | 36 (43.4) | | |
| Ethnicity | | | 0.47 | | | 0.25 | | | 0.81 | 0.60 |
| Hispanic | 126 (38.3) | 203 (61.7) | | 677 (50.6) | 662 (49.4) | | 110 (53.9) | 94 (46.1) | | |
| Non-Hispanic | 426 (40.6) | 622 (59.4) | | 3 (100.0) | 0 (0.0) | | 589 (52.8) | 527 (47.2) | | |
| Missing | 9 (27.3) | 24 (72.7) | | 5 (71.4) | 2 (28.6) | | 5 (83.3) | 1 (16.7) | | |
| Years of education | | | 0.34 | | | 0.04 | | | 0.002 | 0.28 |
| ≤12 years | 318 (38.6) | 506 (61.4) | | 461 (53.1) | 407 (46.9) | | 151 (50.5) | 148 (49.5) | | |
| 13–15 years | 75 (38.3) | 121 (61.7) | | 54 (41.9) | 75 (58.1) | | 408 (57.5) | 302 (42.5) | | |
| ≥16 years | 164 (42.8) | 219 (57.2) | | 165 (48.7) | 174 (51.3) | | 143 (45.8) | 169 (54.2) | | |
| Missing | 4 (57.1) | 3 (42.9) | | 5 (38.5) | 8 (61.5) | | 2 (40.0) | 3 (60.0) | | |
| Marital status | | | 0.0002 | | | 0.01 | | | <.0001 | <.0001 |
| Single | 219 (36.9) | 374 (63.1) | | 159 (50.0) | 159 (50.0) | | 523 (56.7) | 399 (43.3) | | |
| Married/cohabiting | 300 (44.8) | 369 (55.2) | | 502 (52.3) | 458 (47.7) | | 120 (48.8) | 126 (51.2) | | |
| Divorced/separated/widowed | 40 (28.2) | 102 (71.8) | | 21 (33.3) | 42 (66.7) | | 57 (38.0) | 93 (62.0) | | |
| Missing | 2 (33.3) | 4 (66.7) | | 3 (37.5) | 5 (62.5) | | 4 (50.0) | 4 (50.0) | | |
| Current smoker | | | 0.01 | | | 0.04 | | | <.0001 | <.0001 |
| Current | 85 (32.6) | 176 (67.4) | | 198 (46.0) | 232 (54.0) | | 115 (42.6) | 155 (57.4) | | |
| Former | 116 (45.5) | 139 (54.5) | | 153 (51.3) | 145 (48.7) | | 92 (43.6) | 119 (56.4) | | |
| Never | 357 (40.2) | 531 (59.8) | | 331 (53.9) | 283 (46.1) | | 495 (59.0) | 344 (41.0) | | |
| Missing | 3 (50.0) | 3 (50.0) | | 3 (42.9) | 4 (57.1) | | 2 (33.3) | 4 (66.7) | | |
| Monthly alcohol | | | 0.52 | | | 0.07 | | | 0.16 | <.0001 |
| 0 drinks | 1 (100.0) | 0 (0.0) | | 0 (0.0) | 0 (0.0) | | 1 (100.0) | 0 (0.0) | | |
| 1–30 drinks | 330 (35.7) | 594 (64.3) | | 463 (50.2) | 460 (49.8) | | 538 (52.2) | 492 (47.8) | | |
| 31+ drinks | 11 (35.5) | 20 (64.5) | | 10 (32.3) | 21 (67.7) | | 2 (25.0) | 6 (75.0) | | |
| Missing | 219 (48.2) | 235 (51.8) | | 212 (53.7) | 183 (46.3) | | 163 (56.8) | 124 (43.2) | | |
| Sexual orientation | | | 0.38 | | | 0.56 | | | 0.01 | 0.02 |
| MSW | 332 (40.3) | 491 (59.7) | | 532 (50.2) | 527 (49.8) | | 538 (51.0) | 517 (49.0) | | |
| MSM | 41 (38.7) | 65 (61.3) | | 8 (38.1) | 13 (61.9) | | 18 (66.7) | 9 (33.3) | | |
| MSMW | 127 (38.7) | 201 (61.3) | | 50 (49.0) | 52 (51.0) | | 46 (56.1) | 36 (43.9) | | |
| Virgins | 33 (50.0) | 33 (50.0) | | 43 (55.1) | 35 (44.9) | | 59 (67.0) | 29 (33.0) | | |
| Missing | 28 (32.2) | 59 (67.8) | | 52 (58.4) | 37 (41.6) | | 43 (58.1) | 31 (41.9) | | |
| Circumcised | | | 0.07 | | | 0.88 | | | 0.002 | 0.49 |
| No | 458 (38.7) | 724 (61.3) | | 578 (50.7) | 563 (49.3) | | 153 (61.9) | 94 (38.1) | | |
| Yes | 103 (45.2) | 125 (54.8) | | 107 (51.4) | 101 (48.6) | | 551 (51.1) | 528 (48.9) | | |
| Lifetime number of female partners | | | <.0001 | | | <.0001 | | | <.0001 | <.0001 |
| 0–1 | 114 (51.4) | 108 (48.6) | | 138 (62.2) | 84 (37.8) | | 211 (76.7) | 64 (23.3) | | |
| 2–9 | 202 (50.0) | 202 (50.0) | | 383 (54.0) | 326 (46.0) | | 312 (61.4) | 196 (38.6) | | |
| 10–49 | 173 (31.5) | 376 (68.5) | | 111 (34.7) | 209 (65.3) | | 133 (32.9) | 271 (67.1) | | |
| 50+ | 37 (31.1) | 82 (68.9) | | 5 (31.3) | 11 (68.8) | | 29 (31.2) | 64 (68.8) | | |
| Refused | 35 (30.2) | 81 (69.8) | | 48 (58.5) | 34 (41.5) | | 19 (41.3) | 27 (58.7) | | |
| Lifetime number of male partners | | | 0.49 | | | 0.52 | | | 0.09 | 0.96 |
| 0 | 402 (40.0) | 602 (60.0) | | 633 (51.3) | 602 (48.7) | | 647 (52.6) | 583 (47.4) | | |
| 1–9 | 86 (36.1) | 152 (63.9) | | 41 (48.2) | 44 (51.8) | | 38 (64.4) | 21 (35.6) | | |
| 10+ | 57 (44.2) | 72 (55.8) | | 5 (35.7) | 9 (64.3) | | 7 (36.8) | 12 (63.2) | | |
| Missing | 16 (41.0) | 23 (59.0) | | 6 (40.0) | 9 (60.0) | | 12 (66.7) | 6 (33.3) | | |

[a]*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.

[b]Global *P* values were calculated using the Wald chi-square tests comparing the characteristics of men with and without HPV across the three countries. Missing values were not included in *P*-value calculations.

comparable between the three countries ($P = 0.66$). Men from Brazil (18.2%) and the United States (16.4%) have a higher proportion of having one of the 4vHPV types detected at the genitals compared with men from Mexico (13.9%). The prevalence of 4vHPV types and non-4vHRHPV types by age category and country is presented in Fig. 1A. In Brazil, the prevalence of 4vHPV types seems to decrease with age, and we did not see this similar trend in Mexico or the United States. In contrast, the prevalence of the non-4vHPV types by country and age is surprisingly high in the oldest age group 60+ in all three countries and is lowest among the 18 to 19 year olds in Mexico and the United States compared with the older ages. The prevalence of

**Table 2.** Type distribution of prevalent HPV infections overall and by country among 4,085 HIM Study participants

| HPV type | Brazil ($n = 1410$) N (%) | Mexico ($n = 1349$) N (%) | United States ($n = 1326$) N (%) | $P^a$ |
|---|---|---|---|---|
| Any | 849 (60.2) | 664 (49.2) | 622 (46.9) | <**0.001** |
| HR | 472 (33.5) | 365 (27.1) | 373 (28.1) | <**0.001** |
| 16 | 130 (9.2) | 75 (5.6) | 112 (8.4) | <**0.001** |
| 18 | 32 (2.3) | 20 (1.5) | 43 (3.2) | **0.01** |
| 31 | 30 (2.1) | 22 (1.6) | 21 (1.6) | 0.51 |
| 33 | 15 (1.1) | 5 (0.4) | 4 (0.3) | **0.02** |
| 35 | 38 (2.7) | 7 (0.5) | 21 (1.6) | <**0.001** |
| 39 | 52 (3.7) | 51 (3.8) | 40 (3.0) | 0.50 |
| 45 | 28 (2.0) | 15 (1.1) | 25 (1.9) | 0.13 |
| 51 | 95 (6.7) | 85 (6.3) | 79 (6.0) | 0.71 |
| 52 | 64 (4.5) | 53 (3.9) | 42 (3.2) | 0.18 |
| 56 | 40 (2.8) | 20 (1.5) | 14 (1.1) | **0.002** |
| 58 | 54 (3.8) | 30 (2.2) | 14 (1.1) | <**0.001** |
| 59 | 74 (5.2) | 75 (5.6) | 78 (5.9) | 0.77 |
| 68 | 32 (2.3) | 28 (2.1) | 35 (2.6) | 0.62 |
| LR | 688 (48.8) | 534 (39.6) | 453 (34.2) | <**0.001** |
| 6 | 95 (6.7) | 82 (6.1) | 79 (6.0) | 0.66 |
| 11 | 20 (1.4) | 29 (2.1) | 6 (0.5) | <**0.001** |
| 26 | 5 (0.4) | 0 (0.0) | 3 (0.2) | 0.10 |
| 40 | 30 (2.1) | 23 (1.7) | 13 (1.0) | **0.05** |
| 42 | 27 (1.9) | 17 (1.3) | 13 (1.0) | 0.11 |
| 53 | 109 (7.7) | 51 (3.8) | 70 (5.3) | <**0.001** |
| 54 | 36 (2.6) | 25 (1.9) | 30 (2.3) | 0.46 |
| 55 | 40 (2.8) | 35 (2.6) | 25 (1.9) | 0.24 |
| 61 | 98 (7.0) | 65 (4.8) | 27 (2.0) | <**0.001** |
| 62 | 154 (10.9) | 87 (6.4) | 89 (6.7) | <**0.001** |
| 64 | 1 (0.1) | 2 (0.1) | 1 (0.1) | 0.85 |
| 66 | 79 (5.6) | 55 (4.1) | 79 (6.0) | **0.06** |
| 67 | 9 (0.6) | 7 (0.5) | 4 (0.3) | 0.44 |
| 69 | 4 (0.3) | 2 (0.1) | 2 (0.2) | 0.75 |
| 70 | 51 (3.6) | 28 (2.1) | 24 (1.8) | **0.007** |
| 71 | 24 (1.7) | 36 (2.7) | 1 (0.1) | <**0.001** |
| 72 | 29 (2.1) | 13 (1.0) | 10 (0.8) | **0.006** |
| 73 | 48 (3.4) | 11 (0.8) | 16 (1.2) | <**0.001** |
| 81 | 63 (4.5) | 46 (3.4) | 17 (1.3) | <**0.001** |
| 82 | 10 (0.7) | 7 (0.5) | 15 (1.1) | 0.19 |
| 82s[b] | 20 (1.4) | 3 (0.2) | 5 (0.4) | <**0.001** |
| 83 | 43 (3.0) | 35 (2.6) | 36 (2.7) | 0.75 |
| 84 | 123 (8.7) | 104 (7.7) | 103 (7.8) | 0.56 |
| 89 | 107 (7.6) | 80 (5.9) | 93 (7.0) | 0.22 |
| 4vHPV[c] | 256 (18.2) | 187 (13.9) | 217 (16.4) | **0.009** |
| 9vHPV[d] | 376 (26.7) | 268 (19.9) | 278 (21.0) | <**0.001** |

Abbreviations: HR, high-risk HPV types, LR, low-risk HPV types.
[a]*P* value calculated using the Fisher exact test comparing HPV prevalence in all three countries. Values in bold denote statistical significance.
[b]HPV 82 subtype IS39.
[c]4vHPV: one or more of the 4-valent HPV vaccine types (6, 11, 16, 18).
[d]9vHPV: one or more of the 4-valent HPV vaccine types (6, 11, 16, 18, 31, 33, 45, 52, 58).

9vHPV types and non-9vHRHPV types by age category and country is presented in Fig. 1B. Non-9vHRHPV prevalence seemed to stay consistent across the age groups in all three countries.

Factors associated with a prevalent HPV infection by country are shown in Table 3 and all final models were adjusted for age in each country. Final models for the prevalence of any HPV in each country were independently associated with increasing number of lifetime female sexual partners: adjusted PR (aPR) = 1.47; 95% CI, 1.22 to 1.77 in Brazil, aPR = 1.90; 95% CI, 1.23 to 2.93 in Mexico, and aPR = 4.44; 95% CI, 2.92 to 6.76 in the United States, comparing 50 or more lifetime female sexual partners compared with one or less female sexual partner (Table 3). Other factors associated with genital HPV prevalence varied from country to country. In Brazil, prevalence of HPV was associated with being divorced/separated/widowed (aPR = 1.18; 95% CI, 1.0–1.35) compared with being single, and having more than 31 alcohol drink per month (aPR = 1.20; 95% CI, 1.06–1.36) compared with no alcohol drinks. In Mexico, increasing number of recent female sex partners in the past 6 months (more than 3 partners compared to none, aPR = 1.47; 95% CI, 1.22–1.77) and MSM compared with MSW (aPR = 1.90; 95% CI, 1.16–3.11) was also associated with prevalence of HPV. Having at least one male anal sex partner in the past six months (aPR = 1.98; 95% CI, 1.26–3.10) and being a virgin (aPR = 2.13; 95% CI, 1.30–3.47) compared to MSW was associated with HPV prevalence in the United States. Not being circumcised in the United States was associated with lower HPV prevalence (aPR = 0.83; 95% CI, 0.70–0.98).

### Incidence

The median follow-up time for men from Brazil was 49.9 months [interquartile range (IQR) = 47.7–52.9], 47.6 months (IQR = 29.4–55.0) for men from Mexico, and 43.2 months (IQR = 12.8–50.4) for men from the United States. Among the 4,085 men, 86% from Brazil, 65% from Mexico, and 66% from the United States had an incident HPV (any type) infection during follow-up. Table 4 is describing differences in demographic and sexual characteristics at baseline associated with any HPV incidence. In all three countries, lifetime number of female sexual partners and marital status were significantly associated with any HPV incidence (Table 4). Lifetime number of male sexual partners and sexual orientation was significantly associated with any HPV incidence in Brazil and Mexico but not in the United States. HPV incidence was significantly associated with alcohol consumption in Mexico and the United States, but not in Brazil. Although in the United States, HPV incidence was associated with race ($P$ = <0.0001) and smoking status ($P$ = 0.02). When comparing demographic and sexual characteristics across the three countries, race ($P < 0.0001$), marital status ($P < 0.0001$), smoking status ($P < 0.0001$), alcohol consumption ($P < 0.0001$), sexual orientation ($P < 0.0001$), and total number of female sexual partners ($P < 0.0001$) were differentially associated with HPV incidence (Table 4, global $P$ value).

Incidence rates (IR) per 1,000 person-months (pm) for HPV are presented for each country (Table 5) and IRRs were calculated to compare the rates between countries. Any HPV incidence was significantly higher among men from Brazil compared with men from the United States (IRR = 1.5; 95% CI, 1.3–1.7) and significantly lower among men from Mexico compared with men from the United States (IRR = 0.7; 95% CI = 0.6–0.8). No difference in HPV 16 incidence was observed between Brazil and the United States; however, HPV16 incidence in Mexico was significantly lower than the United States (IRR = 0.6; 95% CI, 0.5–0.7). The incidence of HPV6 was significantly higher among men from Brazil compared to men from the United States (IRR = 1.3; 95% CI, .0–1.6); no difference between Mexico and the United States was observed. Similar country trends were observed for HPV11 incidence. In general, Brazil had the highest incidence of other HPV types compared with the United States and Mexico generally had the lowest HPV incidence.

### Clearance

Significant country differences in median duration of genital HPV infections (time to clearance) were observed for all grouped infections (any HPV, LR-HPV, HR-HPV, 4vHPV, and 9vHPV) with

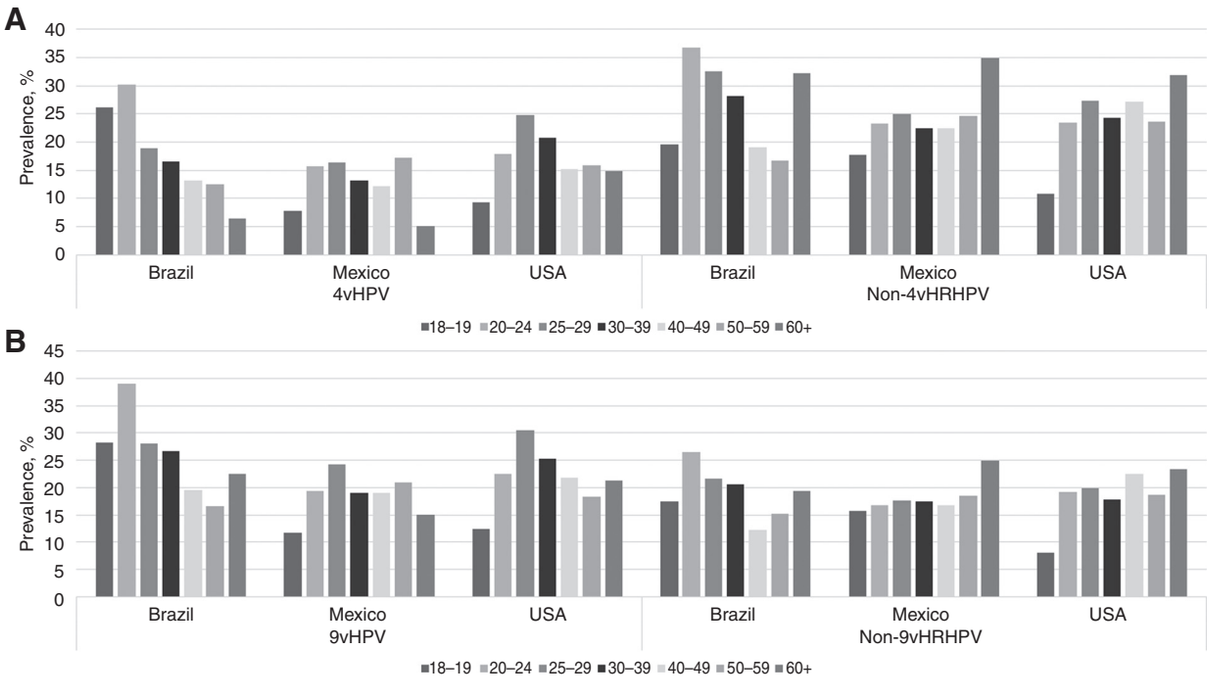


**Figure 1.**

Prevalence of genital HPV by country and age category at baseline. **A,** 4vHPV and non-4vHRHPV **B,** 9vHPV and non-9vHRHPV. Categories for 4vHPV, non-4vHPV, 9vHPV, and non-9vHPV are not mutually exclusive.

an overall trend of Brazil and the United States having lower median infection duration compared with Mexico (Table 5). HPV16 infection median duration was slightly longer in Brazil compared with Mexico and the United States ($P = 0.04$), whereas HPV6 infection median duration was slightly longer in the United States compared to Brazil and Mexico ($P = 0.03$). There were no statically significant differences in median infection duration for HPV11 between the three countries ($P = 0.17$).

## Discussion

In this multinational cohort of 4,085 men followed for a median of 48 months, we compared the natural history of genital HPV infection between the three countries: Brazil, Mexico, and United States. The prevalence and incidence of the genital HPV types known to cause disease in males (16 and 6) was significantly higher among men from Brazil than men from Mexico. Prevalence and incidence of those genital HPV types in the United States varied between being comparable with those of Mexico or Brazil. Although genital HPV16 duration was significantly longer in Brazil ($P = 0.04$) compared with Mexico and the United States, HPV6 duration was shortest in Brazil ($P = 0.03$) compared with Mexico and the United States. Genital HPV infection prevalence, incidence, and duration of the infection as well as risk factors associated with the prevalence of HPV significantly differed by country.

In a 2006 systematic review of the literature, there were 40 studies worldwide that evaluated the prevalence of male genital HPV (14). Overall, HPV prevalence ranged from 1.3% to 72.9% with the majority of studies reporting ≥20%. We found that the prevalence of any genital HPV type was 60.2%, 49.2%, and 46.9% among men from Brazil, Mexico, and the United States, respectively. The differences in prevalence between studies and countries may be due to sampling methods and processing, and the HPV genotyping method used in which a varying number of HPV genotypes are detected. In our study, we assessed the prevalence of 37 HPV genotypes and categorized "any HPV" as being positive for one more of those 37 types where other studies categorized "any HPV" based on being positive to one or more of two HPV types (HPV6 or 16) or 25 different HPV genotypes (14). Assessing genotype-specific prevalence and incidence removes the limitation of using different HPV genotyping platforms. In the HIM Study, HPV16 prevalence was 9.2%, 5.6%, and 8.4% in Brazil, Mexico, and the United States, respectively. HPV6 prevalence in the HIM Study was 6.7%, 6.1%, and 6.0% in Brazil, Mexico and the United States, respectively. In the licensing trial for 4vHPV in males, prevalence of genital HPV6 was 3.4% overall and 3.9% in North America and 3.3% in Latin America (15). HPV16 prevalence was 3.8% overall and 4.5% in North America and 3.9% in Latin America (15). The men participating in the licensing trial were young (16–24 years old), heterosexual, and had between one and five female lifetime sexual partners (15) where men in the HIM Study had a wide age range, all sexualities, and a larger range in the number of sexual partners. These differences in demographic and sexual characteristics may explain why the country-specific prevalence of HPV6 and 16 is so much higher among men in the HIM Study compared with the licensing trial for 4vHPV, given that the sampling methods and HPV genotyping methods were similar between the two studies.

Several factors associated with HPV prevalence differed by country of residence. As expected, we found that increasing number of female sexual partners was associated with higher

**Table 3.** Factors associated with a prevalent infection (any HPV) by country

| | Brazil ($n = 1,410$) | | Mexico ($n = 1,349$) | | United States ($n = 1,326$) | |
|---|---|---|---|---|---|---|
| | uPR | aPR | uPR | aPR | uPR | aPR |
| Age | | | | | | |
| 18–30 | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| 31–44 | 0.96 (0.88–1.05) | 0.95 (0.86–1.05) | 0.99 (0.88–1.12) | 0.99 (0.88–1.12) | 1.36 (1.20–1.55) | 0.98 (0.86–1.13) |
| 45–74 | 0.8 (0.69–0.94) | 0.75 (0.63–0.90) | 1.04 (0.88–1.23) | 1.03 (0.87–1.22) | 1.36 (1.17–1.58) | 0.99 (0.84–1.16) |
| Ethnicity | | | | | | |
| Hispanic | 1.00 (ref) | | 1.00 (ref) | | 1.00 (ref) | |
| Non-Hispanic | 0.96 (0.87–1.06) | | NE | | 1.02 (0.87–1.20) | |
| Race | | | | | | |
| White | 1.00 (ref) | | 1.00 (ref) | | 1.00 (ref) | |
| Black | 0.93 (0.84–1.02) | | 1.23 (0.54–2.82) | | 1.18 (1.03–1.34) | |
| Asian/PI | 1.03 (0.75–1.42) | | NE | | 0.35 (0.22–0.55) | |
| Other | 1.02 (0.85–1.22) | | 0.9 (0.73–1.13) | | 0.86 (0.60–1.25) | |
| Refused | 0.91 (0.69–1.19) | | 0.88 (0.62–1.23) | | 0.9 (0.70–1.16) | |
| Education | | | | | | |
| ≤12 years | 1.00 (ref) | | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | |
| 13–15 years | 1.01 (0.89–1.14) | | 1.24 (1.05–1.46) | 1.17 (1.00–1.37) | 0.86 (0.74–0.99) | |
| ≥16 years | 0.93 (0.84–1.03) | | 1.09 (0.97–1.24) | 1.02 (0.90–1.16) | 1.09 (0.94–1.28) | |
| Marital status | | | | | | |
| Single | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | | 1.00 (ref) | |
| Married/cohabiting | 0.87 (0.80–0.96) | 0.91 (0.82–1.00) | 0.95 (0.84–1.08) | | 1.18 (1.03–1.36) | |
| Divorced/separated/widowed | 1.14 (1.01–1.28) | 1.18 (1.02–1.35) | 1.33 (1.08–1.64) | | 1.43 (1.24–1.66) | |
| Smoking status | | | | | | |
| Never | 1.00 (ref) | | 1.00 (ref) | | 1.00 (ref) | |
| Current | 1.13 (1.02–1.25) | | 1.17 (1.04–1.32) | | 1.40 (1.23–1.60) | |
| Former | 0.91 (0.80–1.03) | | 1.06 (0.91–1.22) | | 1.38 (1.19–1.59) | |
| Monthly alcohol intake | | | | | | |
| 0 drinks | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | | 1.00 (ref) | |
| 1–30 drinks | 1.23 (1.10–1.38) | 1.18 (1.05–1.32) | 1.1 (0.95–1.27) | | 1.02 (0.86–1.21) | |
| 31+ drinks | 1.33 (1.18–1.50) | 1.20 (1.06–1.36) | 1.21 (1.02–1.42) | | 1.24 (1.06–1.46) | |
| Circumcised | | | | | | |
| Yes | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | | 1.00 (ref) | 1.00 (ref) |
| No | 1.12 (0.98–1.27) | 1.12 (0.99–1.27) | 1.02 (0.87–1.18) | | 0.78 (0.66–0.92) | 0.83 (0.70–0.98) |
| Lifetime number of female sex partners | | | | | | |
| 0–1 | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| 2–9 | 1.03 (0.87–1.21) | 1.08 (0.91–1.28) | 1.22 (1.01–1.46) | 1.4 (1.06–1.84) | 1.66 (1.30–2.11) | 2.45 (1.63–3.67) |
| 10–49 | 1.41 (1.22–1.63) | 1.44 (1.23–1.68) | 1.73 (1.43–2.08) | 1.85 (1.39–2.47) | 2.88 (2.30–3.61) | 4.32 (2.90–6.44) |
| 50+ | 1.42 (1.18–1.70) | 1.47 (1.22–1.77) | 1.82 (1.25–2.63) | 1.90 (1.23–2.93) | 2.96 (2.29–3.81) | 4.44 (2.92–6.76) |
| Refused | 1.44 (1.20–1.72) | 1.40 (1.14–1.73) | 1.10 (0.81–1.49) | 1.35 (0.73–2.49) | 2.52 (1.82–3.49) | 1.25 (0.17–9.10) |
| Lifetime number of male anal sex partners | | | | | | |
| 0 | 1.00 (ref) | | 1.00 (ref) | | 1.00 (ref) | |
| 1–9 | 1.07 (0.96–1.19) | | 1.06 (0.86–1.31) | | 0.75 (0.53–1.06) | |
| 10+ | 0.93 (0.79–1.09) | | 1.32 (0.89–1.96) | | 1.33 (0.94–1.89) | |
| Missing | 0.98 (0.75–1.28) | | 1.23 (0.81–1.87) | | 0.70 (0.36–1.36) | |
| Recent number of female sex partners in past 6 months | | | | | | |
| None | 1.00 (ref) | | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | |
| 1 | 1.02 (0.90–1.16) | | 1.14 (0.99–1.31) | 1.13 (0.97–1.32) | 1.33 (1.12–1.56) | |
| 2 | 1.34 (1.18–1.52) | | 1.53 (1.31–1.78) | 1.36 (1.14–1.62) | 1.49 (1.20–1.86) | |
| 3+ | 1.43 (1.28–1.61) | | 1.67 (1.41–1.98) | 1.40 (1.16–1.70) | 1.97 (1.66–2.35) | |
| Refused | 1.39 (1.15–1.70) | | 1.16 (0.90–1.48) | 1.19 (0.86–1.65) | 1.75 (1.18–2.60) | |
| Recent number of male anal sex partners in past 6 months | | | | | | |
| None | 1.00 (ref) | | 1.00 (ref) | | 1.00 (ref) | 1.00 (ref) |
| 1+ | 1.03 (0.91–1.16) | | 1.02 (0.7–1.48) | | 1.04 (0.76–1.43) | 1.98 (1.26–3.10) |
| Sexual orientation | | | | | | |
| MSW | 1.00 (ref) | | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| MSM | 1.03 (0.87–1.21) | | 1.24 (0.88–1.75) | 1.90 (1.16–3.11) | 0.68 (0.40–1.16) | 1.29 (0.59–2.83) |
| MSMW | 1.03 (0.93–1.14) | | 1.02 (0.84–1.25) | 0.94 (0.77–1.15) | 0.90 (0.70–1.15) | 0.69 (0.51–0.93) |
| Virgins | 0.84 (0.65–1.07) | | 0.90 (0.70–1.16) | 1.54 (1.08–2.20) | 0.67 (0.50–0.91) | 2.13 (1.30–3.47) |

NOTE: 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 $P < 0.05$.

HPV prevalence in all three countries. In Brazil, higher HPV prevalence was also significantly associated with being divorced/separated/widowed compared with single. Mexico and the United States saw a similar trend of increasing HPV prevalence in the "recently single" group; however, this variable was not retained in the final multivariable model. "Recently single" men were likely exposed to new HPV types after ending a relationship. In Mexico and the United States, MSM and virgins had a

**Table 4.** Demographic characteristics of 4,085 HIM study participants at baseline comparing men with and without an incident HPV infection during follow-up by country

| | Brazil ($n = 1{,}410$) | | | Mexico ($n = 1{,}349$) | | | United States ($n = 1{,}326$) | | | Global |
|---|---|---|---|---|---|---|---|---|---|---|
| **Factors** | **No infection** | **Infection** | ***P*-value[a]** | **No infection** | **Infection** | ***P*-value[a]** | **No infection** | **Infection** | ***P*- value[a]** | ***P*-value[b]** |
| Age | | | 0.75 | | | 0.29 | | | 0.06 | 0.33 |
| 18–30 | 73 (13.1) | 484 (86.9) | | 201 (36.0) | 357 (64.0) | | 316 (36.2) | 556 (63.8) | | |
| 31–44 | 96 (14.2) | 579 (85.8) | | 224 (36.4) | 391 (63.6) | | 81 (28.8) | 200 (71.2) | | |
| 45–74 | 27 (15.2) | 151 (84.8) | | 53 (30.1) | 123 (69.9) | | 55 (31.8) | 118 (68.2) | | |
| Race | | | 0.76 | | | 0.82 | | | <.0001 | <.0001 |
| White | 121 (14) | 741 (86) | | 23 (31.9) | 49 (68.1) | | 289 (32.7) | 595 (67.3) | | |
| Black | 51 (12.6) | 354 (87.4) | | 1 (33.3) | 2 (66.7) | | 64 (28.1) | 164 (71.9) | | |
| Asian/PI | 4 (18.2) | 18 (81.8) | | 0 (0.0) | 0 (0.0) | | 53 (58.9) | 37 (41.1) | | |
| Other | 12 (15.4) | 66 (84.6) | | 430 (35.4) | 785 (64.6) | | 17 (41.5) | 24 (58.5) | | |
| Refused | 8 (18.6) | 35 (81.4) | | 24 (40.7) | 35 (59.3) | | 29 (34.9) | 54 (65.1) | | |
| Ethnicity | | | 0.72 | | | 1.00 | | | 0.64 | 0.49 |
| Hispanic | 43 (13.1) | 286 (86.9) | | 475 (35.5) | 864 (64.5) | | 66 (32.4) | 138 (67.6) | | |
| Non-Hispanic | 147 (14.0) | 901 (86.0) | | 1 (33.3) | 2 (66.7) | | 383 (34.3) | 733 (65.7) | | |
| Missing | 6 (18.2) | 27 (81.8) | | 2 (28.6) | 5 (71.4) | | 3 (50.0) | 3 (50.0) | | |
| Years of education | | | 0.19 | | | 0.13 | | | 0.75 | 0.20 |
| ≤12 years | 126 (15.3) | 698 (84.7) | | 313 (36.1) | 555 (63.9) | | 107 (35.8) | 192 (64.2) | | |
| 13–15 years | 21 (10.7) | 175 (89.3) | | 53 (41.1) | 76 (58.9) | | 237 (33.4) | 473 (66.6) | | |
| ≥16 years | 49 (12.8) | 334 (87.2) | | 107 (31.6) | 232 (68.4) | | 106 (34.0) | 206 (66.0) | | |
| Missing | 0 (0.0) | 7 (100.0) | | 5 (38.5) | 8 (61.5) | | 2 (40.0) | 3 (60.0) | | |
| Marital status | | | 0.01 | | | 0.0001 | | | 0.007 | <.0001 |
| Single | 66 (11.1) | 527 (88.9) | | 100 (31.4) | 218 (68.6) | | 337 (36.6) | 585 (63.4) | | |
| Married/cohabiting | 113 (16.9) | 556 (83.1) | | 367 (38.2) | 593 (61.8) | | 77 (31.3) | 169 (68.7) | | |
| Divorced/separated/widowed | 17 (12.0) | 125 (88.0) | | 7 (11.1) | 56 (88.9) | | 36 (24.0) | 114 (76.0) | | |
| Missing | 0 (0.0) | 6 (100.0) | | 4 (50.0) | 4 (50.0) | | 2 (25.0) | 6 (75.0) | | |
| Current smoker | | | 0.12 | | | 0.41 | | | 0.02 | <.0001 |
| Current | 30 (11.5) | 231 (88.5) | | 141 (32.8) | 289 (67.2) | | 89 (33.0) | 181 (67.0) | | |
| Former | 29 (11.4) | 226 (88.6) | | 108 (36.2) | 190 (63.8) | | 55 (26.1) | 156 (73.9) | | |
| Never | 137 (15.4) | 751 (84.6) | | 225 (36.6) | 389 (63.4) | | 306 (36.5) | 533 (63.5) | | |
| Missing | 0 (0.0) | 6 (100.0) | | 4 (57.1) | 3 (42.9) | | 2 (33.3) | 4 (66.7) | | |
| Monthly alcohol | | | 0.10 | | | 0.002 | | | 0.0003 | <.0001 |
| 0 drinks | 64 (16.2) | 330 (83.8) | | 133 (41.0) | 191 (59.0) | | 102 (38.8) | 161 (61.2) | | |
| 1–30 drinks | 84 (14.1) | 510 (85.9) | | 251 (35.8) | 451 (64.2) | | 205 (37.6) | 340 (62.4) | | |
| 31+ drinks | 38 (10.9) | 312 (89.1) | | 66 (26.2) | 186 (73.8) | | 136 (27.6) | 357 (72.4) | | |
| Missing | 10 (13.9) | 62 (86.1) | | 28 (39.4) | 43 (60.6) | | 9 (36.0) | 16 (64.0) | | |
| Sexual orientation | | | 0.01 | | | 0.01 | | | 0.10 | <.0001 |
| MSW | 133 (16.2) | 690 (83.8) | | 376 (35.5) | 683 (64.5) | | 357 (33.8) | 698 (66.2) | | |
| MSM | 9 (8.5) | 97 (91.5) | | 1 (4.8) | 20 (95.2) | | 9 (33.3) | 18 (66.7) | | |
| MSMW | 32 (9.8) | 296 (90.2) | | 30 (29.4) | 72 (70.6) | | 22 (26.8) | 60 (73.2) | | |
| Virgins | 11 (16.7) | 55 (83.3) | | 32 (41) | 46 (59) | | 39 (44.3) | 49 (55.7) | | |
| Missing | 11 (12.6) | 76 (87.4) | | 39 (43.8) | 50 (56.2) | | 25 (33.8) | 49 (66.2) | | |
| Circumcised | | | 1.00 | | | 0.14 | | | 0.27 | 0.10 |
| No | 164 (13.9) | 1018 (86.1) | | 414 (36.3) | 727 (63.7) | | 92 (37.2) | 155 (62.8) | | |
| Yes | 32 (14.0) | 196 (86.0) | | 64 (30.8) | 144 (69.2) | | 360 (33.4) | 719 (66.6) | | |
| Lifetime number of female partners | | | 0.0006 | | | <.0001 | | | <.0001 | <.0001 |
| 0–1 | 38 (17.1) | 184 (82.9) | | 104 (46.8) | 118 (53.2) | | 124 (45.1) | 151 (54.9) | | |
| 2–9 | 76 (18.8) | 328 (81.2) | | 273 (38.5) | 436 (61.5) | | 187 (36.8) | 321 (63.2) | | |
| 10–49 | 52 (9.5) | 497 (90.5) | | 66 (20.6) | 254 (79.4) | | 104 (25.7) | 300 (74.3) | | |
| 50+ | 16 (13.4) | 103 (86.6) | | 1 (6.3) | 15 (93.8) | | 23 (24.7) | 70 (75.3) | | |
| Refused | 14 (12.1) | 102 (87.9) | | 34 (41.5) | 48 (58.5) | | 14 (30.4) | 32 (69.6) | | |
| Lifetime number of male partners | | | 0.007 | | | 0.06 | | | 0.81 | 0.003 |
| 0 | 159 (15.8) | 845 (84.2) | | 447 (36.2) | 788 (63.8) | | 423 (34.4) | 807 (65.6) | | |
| 1–9 | 23 (9.7) | 215 (90.3) | | 24 (28.2) | 61 (71.8) | | 19 (32.2) | 40 (67.8) | | |
| 10+ | 13 (10.1) | 116 (89.9) | | 1 (7.1) | 13 (92.9) | | 5 (26.3) | 14 (73.7) | | |
| Missing | 1 (2.6) | 38 (97.4) | | 6 (40.0) | 9 (60.0) | | 5 (27.8) | 13 (72.2) | | |

[a]*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.

[b]Global *P* values were calculated using the Wald $\chi^2$ tests comparing the characteristics of men with and without HPV across the three countries. Missing values were not included in *p* value calculations.

significantly higher prevalence of HPV compared with MSW, whereas a similar nonsignificant trend with MSM was observed in Brazil. We previously reported that the prevalence of genital HPV was similar between MSM and MSW (22); however, these proportions were not stratified by country of residence as presented here. Interestingly, virgins had a higher prevalence of HPV than did MSW in Mexico and the United States. We recently reported the prevalence and factors associated with HPV among virgins (23). That study found that 25% of virgins had at least one HPV type detected and were likely acquiring HPV through nonpenetrative sexual contact (23). In the United States, not being circumcised was associated with a lower prevalence of HPV even

**Table 5.** Incidence rates and median duration of incident genital HPV infections by country of residence

| | Incidence | | | | | Duration | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Median duration, months (95% CI) | | | |
| HPV | Brazil IR (95%CI) | Mexico IR (95%CI) | United States IR (95%CI) | Brazil vs. United States IRR (95%CI) | Mexico vs. United States IRR (95%CI) | Brazil | Mexico | United States | *P*-value[a] |
| Any | 43.2 (39.4–47.3) | 20.9 (18.8–23.1) | 29.8 (27.0–32.8) | **1.5 (1.3–1.7)** | **0.7 (0.6–0.8)** | 6.6 (6.5–6.7) | 7.0 (6.9–7.3) | 6.5 (6.4–6.6) | <**0.0001** |
| HR | 22.2 (20.4–24.1) | 12.4 (11.2–13.7) | 19.0 (17.3–20.9) | **1.2 (1.0–1.3)** | **0.7 (0.6–0.7)** | 6.7 (6.5–6.9) | 7.1 (6.7–7.8) | 6.4 (6.3–6.5) | <**0.0001** |
| 16 | 4.5 (3.9–5.1) | 2.7 (2.2–3.1) | 4.6 (3.9–5.3) | 1.0 (0.8–1.2) | **0.6 (0.5–0.7)** | 6.7 (6.4–7.2) | 6.6 (6.1–8.4) | 6.6 (6.3–7.3) | **0.04** |
| 18 | 2.3 (2.0–2.8) | 0.8 (0.6–1.1) | 1.9 (1.5–2.4) | 1.2 (0.9–1.6) | **0.4 (0.3–0.6)** | 7.1 (6.3–8.5) | 8.1 (6.2–15.0) | 6.2 (6.2–6.4) | 0.56 |
| 31 | 1.3 (1.0–1.6) | 1.1 (0.9–1.5) | 1.4 (1.1–1.8) | 0.9 (0.7–1.3) | 0.8 (0.6–1.2) | 6.6 (6.0–7.4) | 11.9 (8.3–14.7) | 6.4 (6.0–6.7) | <**0.0001** |
| 33 | 0.6 (0.4–0.8) | 0.2 (0.1–0.3) | 0.4 (0.2–0.6) | 1.6 (0.9–2.8) | **0.4 (0.2–0.9)** | 6.4 (5.8–11.7) | 6.3 (5.0–12.0) | 6.0 (6.0–6.5) | **0.01** |
| 35 | 1.3 (1.0–1.6) | 0.2 (0.1–0.3) | 0.8 (0.6–1.1) | **1.6 (1.1–2.3)** | **0.2 (0.1–0.5)** | 9.4 (6.4–13.1) | 6.6 (5.8–12.0) | 6.9 (6.1–12.0) | **0.03** |
| 39 | 2.1 (1.8–2.5) | 1.7 (1.4–2.1) | 2.6 (2.1–3.1) | 0.8 (0.6–1.1) | **0.7 (0.5–0.9)** | 6.9 (6.1–10.8) | 12.0 (7.0–17.5) | 7.1 (6.4–9.2) | **0.01** |
| 45 | 2.1 (1.8–2.5) | 1.0 (0.7–1.3) | 1.7 (1.3–2.1) | 1.3 (0.9–1.7) | **0.6 (0.4–0.8)** | 6.5 (6.1–7.2) | 6.2 (5.9–7.3) | 6.2 (6.0–6.4) | **0.04** |
| 51 | 4.9 (4.3–5.5) | 2.2 (1.8–2.6) | 4.8 (4.1–5.5) | 1.0 (0.8–1.2) | **0.5 (0.4–0.6)** | 6.7 (6.2–7.5) | 9.4 (7.1–12.7) | 6.4 (6.2–7.2) | **0.0009** |
| 52 | 3.7 (3.2–4.2) | 1.8 (1.5–2.2) | 2.5 (2.1–3.0) | **1.5 (1.2–1.9)** | **0.7 (0.5–1.0)** | 6.8 (6.4–7.7) | 7.0 (6.0–10.8) | 6.2 (6.0–6.4) | **0.0001** |
| 56 | 1.6 (1.3–2.0) | 0.9 (0.6–1.2) | 1.2 (0.9–1.6) | 1.3 (0.9–1.8) | **0.7 (0.5–1.0)** | 8.3 (6.4–11.7) | 6.1 (5.8–9.8) | 6.2 (6.1–6.7) | **0.006** |
| 58 | 2.0 (1.7–2.4) | 1.1 (0.8–1.4) | 1.3 (1.0–1.6) | **1.6 (1.2–2.2)** | 0.9 (0.6–1.2) | 7.2 (6.6–11.0) | 9.2 (6.2–12.5) | 6.6 (6.1–11.7) | 0.39 |
| 59 | 3.2 (2.8–3.7) | 2.7 (2.2–3.2) | 3.7 (3.2–4.4) | 0.9 (0.7–1.1) | **0.7 (0.6–0.9)** | 6.4 (6.0–6.7) | 6.4 (6.0–7.8) | 6.2 (6.2–6.8) | **0.006** |
| 68 | 2.1 (1.8–2.5) | 1.5 (1.2–1.9) | 1.3 (1.0–1.7) | **1.6 (1.2–2.2)** | 1.1 (0.8–1.6) | 6.2 (6.0–6.7) | 6.5 (6.0–7.3) | 6.7 (6.4–8.8) | 0.55 |
| LR | 34.1 (31.2–37.1) | 16.2 (14.6–17.9) | 21.8 (19.8–24) | **1.6 (1.4–1.8)** | **0.7 (0.6–0.9)** | 6.6 (6.4–6.7) | 7 (6.8–7.5) | 6.6 (6.5–6.7) | <**0.0001** |
| 6 | 3.7 (3.2–4.3) | 2.6 (2.2–3.1) | 2.9 (2.4–3.5) | **1.3 (1.0–1.6)** | 0.9 (0.7–1.1) | 6.2 (6.0–6.6) | 6.7 (6.3–7.9) | 6.9 (6.4–7.9) | **0.03** |
| 11 | 1.4 (1.1–1.7) | 0.6 (0.4–0.9) | 0.6 (0.4–0.9) | **2.4 (1.5–3.6)** | 1.1 (0.7–1.8) | 6.3 (6.2–6.9) | 6.9 (6.0–11.5) | 7.1 (6.0–13.6) | 0.17 |
| 26 | 0.5 (0.3–0.7) | 0.1 (0.0–0.2) | 0.3 (0.2–0.5) | 1.7 (0.9–3.3) | **0.2 (0.1–0.6)** | 6.2 (6.0–11.7) | 6.0 (5.8–6.3) | 6.5 (6.2–13.1) | 0.65 |
| 40 | 1.5 (1.2–1.8) | 0.7 (0.5–0.9) | 1.3 (1.0–1.7) | 1.1 (0.8–1.6) | **0.5 (0.3–0.8)** | 7.0 (6.4–8.5) | 6.3 (5.8–12.3) | 6.5 (6.1–12.3) | 0.91 |
| 42 | 1.5 (1.2–1.9) | 0.8 (0.6–1.1) | 1.0 (0.7–1.3) | **1.5 (1.1–2.2)** | 0.8 (0.5–1.2) | 8.2 (6.9–12.0) | 6.9 (6.0–12.8) | 6.5 (6.1–7.6) | <**0.0001** |
| 53 | 4.5 (4.0–5.1) | 2.6 (2.1–3.0) | 3.2 (2.7–3.8) | **1.4 (1.1–1.7)** | **0.8 (0.6–1.0)** | 6.6 (6.2–7.2) | 6.8 (6.1–10.5) | 6.2 (6.0–6.7) | **0.04** |
| 54 | 2.8 (2.4–3.3) | 1.4 (1.1–1.7) | 2.7 (2.3–3.3) | 1.0 (0.8–1.3) | **0.5 (0.4–0.7)** | 6.5 (6.2–8.0) | 10.5 (6.5–15.7) | 6.6 (6.4–8.1) | 0.38 |
| 55 | 2.0 (1.7–2.4) | 0.7 (0.5–0.9) | 1.5 (1.2–2.0) | **1.3 (1.0–1.8)** | **0.4 (0.3–0.6)** | 6.5 (6.2–8.0) | 6.9 (6.2–9.0) | 6.7 (6.2–9.2) | 0.67 |
| 61 | 4.7 (4.1–5.3) | 1.6 (1.2–1.9) | 2.1 (1.7–2.6) | **2.2 (1.7–2.8)** | **0.7 (0.6–1.0)** | 6.3 (6.0–6.8) | 9.7 (6.9–15.0) | 6.6 (6.2–10.6) | **0.01** |
| 62 | 6.1 (5.4–6.8) | 2.0 (1.6–2.4) | 3.8 (3.2–4.5) | **1.6 (1.3–1.9)** | **0.5 (0.4–0.7)** | 6.6 (6.4–7.1) | 6.9 (6.3–9.8) | 6.8 (6.4–8.0) | 0.26 |
| 64 | 0.2 (0.1–0.4) | 0.1 (0.1–0.3) | 0.0 (0.0–0.2) | **5.6 (1.3–24.5)** | 3.2 (0.7–15.0) | 6.0 (5.7–10.6) | 6.0 (5.6–6.4) | 6 (0.6–6.8) | 0.31 |
| 66 | 3.8 (3.3–4.3) | 2.0 (1.6–2.4) | 3.9 (3.3–4.6) | 1.0 (0.8–1.2) | **0.5 (0.4–0.6)** | 6.5 (6.2–7.1) | 10.4 (7.2–11.9) | 6.7 (6.3–7.4) | **0.0006** |
| 67 | 0.8 (0.6–1.1) | 0.5 (0.3–0.7) | 0.5 (0.3–0.8) | **1.7 (1.0–2.8)** | 1.0 (0.6–1.8) | 6.0 (6.0–6.8) | 6.9 (6.2–10.9) | 6.1 (6.0–6.7) | **0.01** |
| 69 | 0.4 (0.2–0.6) | 0.1 (0.0–0.2) | 0.2 (0.1–0.3) | **2.4 (1.0–5.6)** | 0.7 (0.2–2.0) | 5.9 (5.8–6.4) | 6.6 (0.9–17.0) | 6.0 (0.4–7.9) | 0.20 |
| 70 | 2.2 (1.8–2.6) | 0.8 (0.6–1.0) | 0.8 (0.5–1.1) | **2.9 (2.0–4.3)** | 1.0 (0.6–1.6) | 6.3 (6.2–6.7) | 6.7 (6.1–9.6) | 6.4 (6.0–7.2) | 0.99 |
| 71 | 0.9 (0.7–1.2) | 1.0 (0.7–1.3) | 0.2 (0.1–0.4) | **4.2 (2.2–8.2)** | **4.4 (2.2–8.7)** | 7.1 (6.0–12.2) | 6.7 (6.2–12.7) | 6.0 (5.5–20.4) | 0.22 |
| 72 | 1.5 (1.2–1.8) | 0.5 (0.3–0.7) | 0.9 (0.6–1.2) | **1.7 (1.2–2.5)** | **0.6 (0.4–0.9)** | 6.4 (6.1–7.8) | 6.7 (6.1–17.9) | 6.2 (6.0–6.7) | 0.07 |
| 73 | 2.0 (1.6–2.4) | 0.4 (0.3–0.7) | 1.4 (1.1–1.8) | **1.4 (1.0–1.9)** | **0.3 (0.2–0.5)** | 6.7 (6.2–9.2) | 7.9 (6.1–12.4) | 7.1 (6.3–11.8) | 0.54 |
| 81 | 2.7 (2.3–3.2) | 1.3 (1.0–1.7) | 1.0 (0.7–1.3) | **2.8 (2.0–4.0)** | 1.4 (0.9–2.0) | 6.8 (6.5–7.9) | 6.9 (6.3–9.8) | 6.2 (6.2–11.9) | 0.36 |
| 82 | 1.0 (0.7–1.2) | 0.4 (0.2–0.6) | 0.9 (0.6–1.2) | 1.1 (0.7–1.6) | **0.4 (0.3–0.7)** | 6.4 (6.0–6.9) | 7.2 (5.6–13.9) | 6.7 (6.2–12.7) | 0.34 |
| 82s[b] | 0.8 (0.6–1.1) | 0.4 (0.2–0.5) | 0.2 (0.1–0.4) | **4.2 (2.1–8.5)** | 1.8 (0.8–3.9) | 7.5 (6.2–12.2) | 7.6 (6.0–13.3) | 6.0 (0.7–13.6) | 0.12 |
| 83 | 2.1 (1.8–2.5) | 1.0 (0.7–1.3) | 1.4 (1.0–1.8) | **1.6 (1.1–2.1)** | **0.7 (0.5–1.0)** | 7.1 (6.3–8.5) | 6.9 (6.2–13.6) | 6.1 (6.0–6.7) | 0.53 |
| 84 | 5.2 (4.6–5.8) | 2.7 (2.2–3.2) | 5.6 (4.9–6.4) | 0.9 (0.8–1.1) | **0.5 (0.4–0.6)** | 6.9 (6.5–8.0) | 7.8 (6.4–15.3) | 6.5 (6.3–7.6) | **0.003** |
| 89 | 5.6 (5.0–6.3) | 2.7 (2.3–3.2) | 4.5 (3.8–5.2) | **1.3 (1.0–1.5)** | **0.6 (0.5–0.8)** | 6.7 (6.4–7.3) | 6.9 (6.2–8.8) | 7.0 (6.6–9.2) | 0.16 |
| 4vHPV[c] | 10.3 (9.4–11.4) | 6.1 (5.4–6.9) | 8.2 (7.3–9.3) | **1.3 (1.1–1.5)** | **0.7 (0.6–0.9)** | 6.5 (6.3–6.8) | 6.7 (6.4–7.6) | 6.5 (6.4–6.9) | **0.002** |
| 9vHPV[d] | 16.6 (15.2–18.1) | 9.1 (8.1–10.1) | 12.8 (11.5–14.2) | **1.3 (1.1–1.5)** | **0.7 (0.6–0.8)** | 6.6 (6.4–6.8) | 6.9 (6.6–7.8) | 6.4 (6.3–6.5) | <**0.0001** |

NOTE: Values in bold denote statistical significance.

[a]*P* values for grouped infections and type-specific infections were derived from Kaplan–Meier curves of HPV infection clearance comparing the three countries across the entire follow-up period. Values in bold denote statistical significance.

[b]HPV 82 subtype IS39.

[c]4vHPV: one or more of the 4-valent HPV vaccine types (6, 11, 16, 18).

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

after adjusting for potential confounders. Uncircumcised United States males in the HIM Study were more likely to be Asian or other race, and have a fewer number of female sexual partners. When race was forced back into the model for United States, circumcision status was no longer significantly associated with genital HPV.

Similar to genital HPV prevalence, HPV incidence varied by country as well. The incidence rate for any HPV at the genitals was, 51.8, 25.0, and 35.7 per 100 person years (py) among men from Brazil, Mexico, and the United States, respectively. These are similar to estimates provided in a 2016 systematic review of genital HPV incidence and duration (13), which reports incidence rates of any HPV from 14.8 per 100 py among men from Mexico (24) to 46.1 per 100 py among men from the United States (25). Reported duration of any HPV-type infection in the HIM Study (range 6.5–7.0 months) was also comparable with estimates provided in the systematic review by country with duration ranging from 5.1 to 5.9 months (13, 24, 25). The slight variation in duration is likely an arbitrary determent that is based on the time between study visits in each cohort. The majority of men were able to clear their HPV infections within the 6-month time period.

Differences in the genital HPV natural history by country may explain the differences in HPV-related disease outcomes that we and other have observed (11, 26). Within the HIM Study, the incidence of genital warts was similar across the three countries,

but the incidence of penile intraepithelial neoplasia (PeIN) was higher in Brazil than Mexico and the United States, although not statistically significant (26). In this study, we observed Brazil to have the highest prevalence and duration of HPV16 infections, which likely explains the higher rate of infection progression to disease (PeIN). When we assessed the progression of HPV6 infections to HPV6-positive genital warts, we found that Mexico and the United States had higher progression rates of infection than men in Brazil. Although men in Mexico and United States have a lower prevalence and incidence of HPV6 infections, they may be more likely to progress to disease (26). Differences in HPV progression may be due to host or viral differences in each country. We have previously shown that natural immunity to HPV does not prevent genital warts in men so antibody prevalence is not likely the reason for these country differences (27).

This study has several strengths including the large sample size, duration of follow-up, and data collection from three international clinical sites. Data collection and specimen processing were consistent across the three clinical sites. Men were recruited into the HIM Study at a time when HPV vaccination rates were low among females, and only young females were being vaccinated in the United States. Therefore, the prevalence estimates provided by country and age group reflect prevaccination estimates among males, uncontaminated by herd protection. The HIM Study is not a population-based study, but the demographics of the men included at each clinical site are similar to the underlying population of men ages 18 to 70 years in their respective communities (17). Therefore, a potential limitation of the cohort is that the findings may not be generalizable to all men in each country; although, our country-specific data were comparable with findings from others in those specific countries (13, 14). HPV incidence and infection duration was based on clinic visits that occurred every 6 months and may not accurately reflect the exact timing of infection or clearance of the infection. However, given the sample size and duration of follow-up, the 6-month visit timing is cost-effective and still able to capture the natural history of HPV.

In summary, we found that genital HPV natural history differs in the three countries: Brazil, Mexico, and the United States. In general, Brazil had a higher prevalence, incidence, and duration of HPV16 and 6, which are the two predominant types known to cause disease in males compared with men from Mexico and HPV infection in the United States varied between being comparable with those of Mexico or Brazil. Currently, there is no routine screening for genital HPV among males and although HPV is common in men, and most naturally clear the infection, a proportion of men do develop HPV-related diseases. The 4vHPV and 9vHPV vaccines are licensed for the use in males and clinical trials have shown clinical efficacy in preventing disease (28). Globally, only five countries have national gender-neutral vaccine policies: the United States, Austria, Australia, Israel, and some provinces in Canada. Results presented here indicate that men in Brazil and Mexico often have similar, if not higher HPV infections, compared with men from the United States, and may benefit from similar policy measures.

## Disclosure of Potential Conflicts of Interest

S. Sudenga reports receiving a commercial research grant from Merck. L.L. Villa reports receiving other commercial research support from Merck Sharp & Dohme, has received speakers bureau honoraria from Merck Sharp & Dohme, and is a consultant/advisory board member of Merck Sharp & Dohme. A.R. Giuliano reports receiving a commercial research grant from Merck, has received speakers bureau honoraria from Merck, and is a consultant/advisory board member of Merck. No potential conflicts of interest were disclosed by the other authors.

## Disclaimer

The opinions expressed in this paper are those of the authors and do not necessarily represent those of Merck Sharp & Dohme Corp.

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**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** S.L. Sudenga, B.N. Torres, L.L. Villa, E. Lazcano-Ponce, J. Salmeron, A.R. Giuliano
**Writing, review, and/or revision of the manuscript:** S.L. Sudenga, R. Silva, L.L. Villa, E. Lazcano-Ponce, M. Abrahamsen, J. Salmeron, A.R. Giuliano
**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** S.L. Sudenga, L.L. Villa, E. Lazcano-Ponce, M.L. Baggio, M. Quiterio
**Study supervision:** S.L. Sudenga, L.L. Villa, M. Abrahamsen
**Other (study supervision at the Brazilian site only and co-PI of the study):** L.L. Villa

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