MAJOR ARTICLE

Incidence, Clearance, and Disease Progression of Genital Human Papillomavirus Infection in Heterosexual Men

Edson Duarte Moreira Jr,[1] Anna R. Giuliano,[2] Joel Palefsky,[3] Carlos Aranda Flores,[4] Stephen Goldstone,[5] Daron Ferris,[6] Richard J. Hillman,[7] Harald Moi,[8] Mark H. Stoler,[9] Brooke Marshall,[10] Scott Vuocolo,[10] Dalya Guris,[10] and Richard M. Haupt[10]

[1]Associação Obras Sociais Irmã Dulce and Oswaldo Cruz Foundation, Brazilian Ministry of Health, Bahia; [2]Center for Infection Research in Cancer, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida; [3]Department of Medicine, University of California–San Francisco; [4]University Medical Center, National Public Health Institute, Morelos, Mexico; [5]Mount Sinai School of Medicine, New York, New York; [6]Gynecologic Cancer Prevention Center, Georgia Health Sciences University, Augusta; [7]Western Sydney Sexual Health Centre, University of Sydney, Australia; [8]Olafia STI Clinic, Oslo University Hospital, University of Oslo, Norway; [9]University of Virginia, Charlottesville; and [10]Merck, North Wales, Pennsylvania

Background. In this analysis, we examine the incidence and clearance of external genital human papillomavirus (HPV) infection among heterosexual males aged 16–24 years.

Methods. A total of 1732 males aged 16–24 years old in the placebo arm of a quadrivalent HPV vaccine trial were included in this analysis. Participants were enrolled from 18 countries in Africa, the Asia-Pacific region, Europe, Latin America, and North America. Subjects underwent anogenital examinations and sampling of the penis, scrotum, and perineal/perianal regions.

Results. The incidence rate of any HPV DNA genotype 6, 11, 16, and/or 18 detection was 9.0 cases per 100 person-years. Rates of HPV DNA detection were highest in men from Africa. Median time to clearance of HPV genotypes 6, 11, 16, and 18 DNA was 6.1, 6.1, 7.7, and 6.2 months, respectively. Median time to clearance of persistently detected HPV 6, 11, 16, and 18 DNA was 6.7, 3.2, 9.2, and 4.7 months, respectively.

Conclusion. The study results suggest that the acquisition of HPV 6, 11, 16, and/or 18 in males is common and that many of these so-called infections are subsequently cleared, similar to findings for women. Nevertheless, given the high rate of HPV detection among young men, HPV vaccination of males may reduce infection in men and reduce the overall burden of HPV-associated disease in the community.

Keywords. HPV; incidence; progression; males.

Human papillomavirus (HPV) is the most common viral sexually transmitted infection in men and women in many countries, including the United States, where an estimated 6.2 million new cases occur each year [1]. While the impact of HPV infection in women has been well studied, the burden of HPV-associated disease in men is also notable. In males, HPV infection can lead to anogenital condyloma acuminata and cancers of the penis, anus, and oropharynx [2]. Though not confirmed, published data suggest a possible association between HPV infection and cancers of the esophagus and lung [2–7].

HPV can be transmitted to and by both sexes, and data suggest that the epidemiology of genital HPV infection among men is similar to that among women [8–10]. Once HPV infects one sex partner, it is rapidly transmitted to the other [11]. In a 12-month period, the probability of acquiring a new genital HPV infection in men is estimated to be 0.29–0.39 [3, 8–10], which is comparable to previous estimates in women [8–10]. Additionally, the overall transmission rate from one heterosexual partner to the other over a 6-month period has been estimated to be 3.7 cases per 100 person-months [12]. The duration of genital HPV infection in men also appears to be similar to that in women,

Received 25 October 2013; accepted 22 January 2014; electronically published 4 February 2014.

Correspondence: Edson D. Moreira Jr, MD, MPH, PhD, Centro de Pesquisa Gonçalo Moniz, Fundação Oswaldo Cruz, Rua Waldemar Falcão 121, Salvador, Bahia, Brasil, 40.296-710 (edson@bahia.fiocruz.br).

The Journal of Infectious Diseases 2014;210:192–9

DOI: 10.1093/infdis/jiu077

with approximately 70% of both sexes clearing infections within a 12-month period [13]. Interestingly, differences between the age-related prevalence of HPV in men and women have been described [3]. HPV infection rates seem to stay constant in men, independent of age, as opposed to women, among whom the HPV prevalence is highest during 18–24 years of age and then decreases until middle age, after which it generally remains steady (increases in older age groups have been seen in some countries) [11].

Compared with the global data available on HPV in women [14], there are limited HPV infection incidence and prevalence data from population-based samples of men from different geographic areas. Available data suggest that HPV is common among sexually active men but also that there is considerable variation in prevalence and incidence, depending on age, country, and region [3, 8–10, 15–26].

Here we report the incidence rate and the duration of anogenital HPV infections (both any detection and persistent detection) among heterosexual men aged 16–24 years enrolled in the placebo arm of a worldwide double-blinded, randomized, placebo-controlled clinical trial of the quadrivalent HPV vaccine. In addition, differences by anatomic site and geographic region and sociodemographic and sexual behavior factors associated with external genital HPV infection in men were assessed.

METHODS

Subjects

Data were analyzed from men enrolled in the placebo arm of a randomized, double-blind, placebo-controlled clinical trial (protocol 020; clinical trials registration NCT00090285) designed to evaluate the efficacy of the quadrivalent HPV L1 virus-like particle vaccine (which targets HPV genotypes 6, 11, 16, and 18) in young men (Gardasil; Merck, Whitehouse Station, NJ). The study population and trial design have been described in detail elsewhere [27]. Briefly, the trial population consisted of 3463 heterosexual males aged 16–24 years and 602 males who have sex with males, aged 16–27 years, from 71 sites in 18 countries in Africa, the Asia-Pacific region, Europe, Latin America, and North America. Participants were eligible if they were aged 16–24 years, were healthy, and agreed to refrain from sexual activity for 2 calendar days before scheduled visits (to avoid contamination with HPV DNA deposited during intercourse). Heterosexual subjects also had to have had a lifetime number of 1–5 exclusively female sex partners. Subjects with a history of or current clinically detectable anogenital warts or genital lesions suggesting other sexually transmitted diseases were excluded. Subjects were randomly assigned at a ratio of 1:1 to receive quadrivalent HPV vaccine or placebo. Although both heterosexual males and males who have sex with males were enrolled in the trial, only data for the 1732 heterosexual males assigned to the placebo arm are presented here.

All enrolled subjects underwent external genital inspection and swabbing for HPV DNA detection at baseline (day 1) and months 7, 12, 18, 24, 30, and 36. If a lesion observed at baseline was judged by the investigator to be possibly HPV related or of unknown etiology, then the subject was excluded from the study. Subjects with known immunodeficiency or human immunodeficiency virus (HIV) infection were also excluded. Subjects with HIV infection detected after enrollment were not excluded from the study.

Institutional review boards at participating centers approved the protocol, and written informed consent was obtained from all subjects. Studies were conducted in conformity with applicable country or local requirements regarding ethics committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.

Study Measurements

External genital inspection was conducted using a magnifying glass. Swab specimens were collected separately from the penile, scrotal, and perineal/perianal areas at baseline and months 7, 12, 18, 24, 30, and 36 with a wetted Dacron-tipped swab (swab specimens of the anal canal were not taken from heterosexual subjects). All specimens were tested for the β-globin gene (positive control), and adequate samples were tested for a panel of 4 HPV types (ie, HPV 6, 11, 16, and 18). Swab, biopsy, and serum samples were tested at Merck Research Laboratories (Wayne, PA) and Pharmaceutical Product Development (Wilmington, DE).

HPV Testing

Multiplex polymerase chain reaction (PCR) based on real-time fluorescent PCR was used for the detection of HPV 6, 11, 16, and 18 in swab samples [28–30]. This assay allowed for simultaneous detection of 3 gene products (L1, E6, and E7) for a given HPV type. DNA was purified using the QIAmp DNA kit (Qiagen, Germantown, MD). HPV type–specific primers based on published L1, E6, and E7 sequences were used to amplify specific portions of these genes simultaneously. Specific amplicons were detected in real time by fluorescently labeled oligonucleotide probes. The gene specific oligonucleotide probes were each labeled with a different fluorescent label.

Statistical Methods

The analysis of the incidence and clearance of HPV infections was based on HPV test results for the swab samples and thin-section microtomy specimens. Incidence and time to clearance were estimated for vaccine-associated HPV types [6, 11, 16, 18], by group and individually. For estimates of grouped or type-specific HPV incidence, only participants who had negative results of DNA tests for grouped HPV types or a specific HPV type at enrollment were included. Clearance and incidence

rates, by type, were determined using appropriate incidence density calculations based on person-time denominators (ie, person-years). 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. Also, because HPV testing occurred at discrete intervals (typically every 6 months), it is likely that a positive HPV test result observed on a particular date was preceded by an unobserved period of HPV positivity of indeterminate length. For the calculation of person-time at risk, it was therefore assumed that the HPV infection occurred at the midpoint between the date of the initial positive test result and the date of the previous negative test result). Since multiple infections are possible within an individual, multiple positive test results were judged as separate events. The exact 95% confidence interval (CI) calculated for an incidence estimate was based on the number of events modeled as a Poisson variable over the total number of person-years.

Actuarial analysis of mean and median clearance times, by type, took into account censoring for incomplete observations (ie, those in whom clearance had not occurred at the last recorded follow-up visit). Kaplan-Meier curves depicting cumulative incidence were constructed for any HPV and type-specific HPV to derive the above-indicated statistics and rates of cumulative incidence at different points during follow-up time. Factors associated with these outcomes were assessed with proportional hazards regression analysis. A backward-selection method, with a significance threshold of 0.10, was used to identify variables included in the final multivariable model. Candidate variables included race, education, marital status, smoking status, circumcision status, lifetime number of female sex partners, lifetime history of condom use with female sex partners, and number of female partners in the past 6 months. World region (ie, Africa, Asia-Pacific, Europe, Latin America, and North America) and age (in years) were included in all models as design factors. The proportional hazards assumption for the Cox models was tested, and no gross violations were shown.

Any HPV DNA detection was defined as any positive PCR result for an anogenital swab or biopsy specimen taken at one visit. Persistent DNA detection is a subset of this group that was defined as detection of the same HPV type in any anogenital swab or biopsy specimen from the same site collected on ≥2 consecutive visits ≥6 months (±1 month) apart. HPV clearance was defined as a participant testing negative for a specific HPV type at 2 consecutive visits after having a specimen from the same site testing positive for HPV DNA. The time to clearance or duration of an HPV infection was defined as the time elapsed from the date of the first positive HPV test result to the date of the first negative HPV test result after the last detection of HPV infection. Participants whose infection(s) did not clear were censored at the date of the last positive HPV test result.

Table 1. Characteristics of 3463 Heterosexual Males Aged 16–24 Years Who Were Randomly Assigned to Received Quadrivalent Human Papillomavirus Vaccine or Placebo

Characteristic	Vaccine (n = 1742)	Placebo (n = 1721)	Total (n = 3463)
Age, y			
Mean ± SD	20.2 ± 1.8	20.2 ± 1.8	20.2 ± 1.8
Median (range)	20 (15–24)	20 (16–24)	20 (15–24)
Race/ethnicity			
Asian	180 (10.3)	193 (11.2)	373 (10.8)
Black	391 (22.4)	372 (21.6)	763 (22.0)
Hispanic American	321 (18.4)	365 (21.2)	686 (19.8)
Native American	2 (0.1)	1 (0.1)	3 (0.1)
White	563 (32.3)	505 (29.3)	1068 (30.8)
Other	285 (16.4)	285 (16.6)	570 (16.5)
Region			
Africa	277 (15.9)	261 (15.2)	538 (15.5)
Asia-Pacific	125 (7.2)	147 (8.5)	272 (7.9)
Europe	190 (10.9)	184 (10.7)	374 (10.8)
Latin America	703 (40.4)	740 (43.0)	1443 (41.7)
North America	447 (25.7)	389 (22.6)	836 (24.1)
Smoking status			
Current smoker	634 (36.4)	602 (35.0)	1236 (35.7)
Ex-smoker	115 (6.6)	122 (7.1)	237 (6.8)
Never smoked	972 (55.8)	988 (57.4)	1960 (56.6)
Missing or unknown	21 (1.2)	9 (0.5)	30 (0.9)
Circumcision			
Yes	663 (38.1)	613 (35.6)	1276 (36.8)
No	1077 (61.8)	1107 (64.3)	2184 (63.1)
Missing or unknown	2 (0.1)	1 (0.1)	3 (0.1)

Data are no. (%) of subjects, unless otherwise indicated.

RESULTS

Subject demographic characteristics are presented in Table 1. The mean age (±SD) was 20.2±1.8 years, and 43.0% were from Latin America. Smokers comprised 35.0% of enrolled subjects, and 64.3% of subjects were uncircumcised.

As seen in Table 2, the rate of any HPV 6, 11, 16, or 18 DNA detection among males who were seronegative and PCR negative for all 4 HPV types on day 1 was 9.0 cases per 100 person-years at risk. When the incidence rates of HPV infection were stratified by geographic region, some differences became apparent. Similar to what was previously seen among females, Africa (South Africa) had the highest incidence of any HPV 6, 11, 16, or 18 DNA detection (17.2 cases per 100 person-years), while Asia-Pacific had the lowest incidence (3.2 cases per 100 person-years). This pattern was generally similar for the individual HPV types, with the exception of HPV 11. In all other cases, Africa had the largest

Table 2. Incidence Rates of Any Detection of Human Papillomavirus (HPV) Genotypes 6, 11, 16, and/or 18 DNA Among Heterosexual Male Placebo Recipients Who Were Seronegative and Polymerase Chain Reaction Negative for All 4 HPV Types on Day 1

Variable	HPV 6, 11, 16, or 18			HPV 6			HPV 11			HPV 16			HPV 18		
	Subjects, No.	Person-years	Incidence[a]	Subjects, No.	Person-years	Incidence[a]	Subjects, No.	Person-years	Incidence[a]	Subjects, No.	Person-years	Incidence[a]	Subjects, No.	Person-years	Incidence[a]
Overall[b]	282	3119.6	9.0	135	3575.6	3.8	53	3818.1	1.4	158	3542.8	4.5	95	3736.3	2.5
Region															
Africa	73	425.7	17.2	33	529.1	6.2	23	577.6	4.0	39	539.0	7.2	34	550.8	6.2
Asia-Pacific	10	310.2	3.2	3	322.1	0.9	4	329.9	1.2	3	329.7	0.9	3	332.9	0.9
Europe	30	426.0	7.0	15	479.1	3.1	1	496.2	0.2	19	459.0	4.1	10	476.7	2.1
Latin America	119	1395.7	8.5	62	1602.1	3.9	20	1737.2	1.2	61	1603.8	3.8	36	1696.2	2.1
North America	50	562.0	8.9	22	643.2	3.4	5	677.5	0.7	36	611.4	5.9	12	679.7	1.8
Anatomic site															
Penis	255	3114.0	8.2	110	3561.6	3.1	40	3767.7	1.1	153	3492.2	4.4	85	3679.0	2.3
Perineum/anus	136	3136.3	4.3	52	3485.5	1.5	22	3651.8	0.6	75	3451.8	2.2	35	3606.4	1.0
Scrotum	209	3150.6	6.6	81	3557.2	2.3	37	3743.3	1.0	115	3509.8	3.3	63	3683.8	1.7

[a] Per 100 person-years at risk.

[b] Subjects 16–27 years old who were naive to all 4 types (HPV 6, 11, 16, and 18) on day 1.

Figure 1. Cumulative incidence of human papillomavirus (HPV) infection among heterosexual male subjects naive to all vaccine-associated HPV types on day 1. Abbreviation: CI, confidence interval.

incidence of any HPV DNA detection, Asia Pacific had the smallest incidence, and the other regions had intermediate incidences. The rate of any HPV 6, 11, 16, or 18 DNA detection was highest in penile swabs (8.2 cases per 100 person-years), followed by scrotal swabs (6.6 cases per 100 person-years), and perineal/perianal swabs (4.3 cases per 100 person-years; Table 2). The pattern of incidence was typical, with incident HPV 16 detection being most common and incident HPV 11 detection being least common, no matter the anatomic site sampled. The cumulative incidence of HPV 6, 11, 16, or 18 infections among heterosexual subjects naive to all of those types on day 1 rose to near 50% by 48 months (Figure 1). Not surprisingly, the largest proportion of this increase can be attributed to HPV 16, the incidence of which rose to >35% by 48 months.

The duration of any HPV 6, 11, 16, or 18 DNA detection and persistent HPV 6, 11, 16, or 18 DNA detection can be seen in Table 3. The median time to clearance (defined as 2 consecutive negative test results for swab specimens from the same site where HPV DNA was previously detected) of any HPV 6, 11, 16, and 18 DNA detection (Table 3) in all subjects was 6.1, 6.1, 7.7, and 6.2 months, respectively. Results were similar whether subjects had single or multiple HPV types detected, although the median time to clearance was slightly elevated for subjects with multiple HPV types detected.

The median time to clearance (defined as 2 consecutive, negative swab test results) of persistent HPV 6, 11, 16, and 18 infections (Table 3) was 6.7, 3.2, 9.2, and 4.7 months, respectively. Mean and median times to clearance of persistent HPV 6 and 11 detection were similar in subjects with single or multiple HPV types detected. At 24 months after the first detection of persistent DNA detection, 5.0%, 0.0%, 8.6%, and 3.9% of subjects still had HPV 6, 11, 16, and 18, DNA detected, respectively.

Table 3. Duration and Clearance of Any Detected Human Papillomavirus (HPV) DNA and Persistently Detected HPV DNA Among Heterosexual Male Placebo Recipients Who Were Seronegative and Polymerase Chain Reaction Negative for All 4 HPV Types on Day 1

		Time to Clearance							
HPV Type	Subjects, No.	Mo, Median	Mo, Mean	6 mo, Subjects, %	12 mo, Subjects, %	18 mo, Subjects, %	24 mo, Subjects, %	30 mo, Subjects, %	36 mo, Subjects, %
Any DNA detection[a]									
All subjects									
HPV 6	135	6.1	7.6	49.6	34.8	8.9	5.2	0.0	1.5
HPV 11	53	6.1	7.0	47.2	39.6	9.4	3.8	0.0	0.0
HPV 16	158	7.7	9.5	36.7	38.6	15.8	4.4	3.2	1.3
HPV 18	95	6.2	7.9	41.1	44.2	8.4	4.2	2.1	0.0
Subjects with single HPV type detected									
HPV 6	79	5.9	7.2	53.2	34.2	8.9	2.5	0.0	1.3
HPV 11	26	6.1	6.3	46.2	42.3	11.5	0.0	0.0	0.0
HPV 16	102	7.0	9.5	38.2	37.3	14.7	3.9	3.9	2.0
HPV 18	47	6.1	7.6	44.7	40.4	8.5	4.3	2.1	0.0
Subjects with multiple HPV types detected									
HPV 6	56	6.1	8.1	44.6	35.7	8.9	8.9	0.0	1.8
HPV 11	27	6.3	7.6	48.2	37.0	7.4	7.4	0.0	0.0
HPV 16	56	8.8	9.4	33.9	41.1	17.9	5.4	1.8	0.0
HPV 18	48	6.8	8.1	37.5	47.9	8.3	4.2	2.1	0.0
Persistent DNA detection[b,c]									
All subjects									
HPV 6	40	6.7	11.1	42.5	27.5	7.5	5.0	10.0	7.5
HPV 11	9	3.2	4.6	66.6	33.3	0.0	0.0	0.0	0.0
HPV 16	58	9.2	13.2	36.2	24.1	10.3	8.6	8.6	8.6
HPV 18	26	4.7	8.8	53.9	23.1	11.5	3.9	3.9	0.0
Subjects with single HPV type detected									
HPV 6	32	6.9	11.1	43.8	25.0	9.4	6.3	9.4	6.3
HPV 11	4	2.9	4.5	75.0	25.0	0.0	0.0	0.0	0.0
HPV 16	50	9.5	13.4	36.0	22.0	12.0	8.00	10.0	8.0
HPV 18	18	5.3	9.0	50.0	27.8	11.1	5.6	0.0	0.0
Subjects with multiple HPV types detected									
HPV 6	8	6.4	11.3	37.5	37.5	0.0	0.0	12.5	12.5
HPV 11	5	3.5	4.8	60.0	40.0	0.0	0.0	0.0	0.0
HPV 16	8	7.2	11.9	37.5	37.5	0.0	12.5	0.0	12.5
HPV 18	8	4.6	8.3	62.5	12.5	12.5	0.0	12.5	0.0

Truncation occurred at the time disease was diagnosed.

[a] Clearance was defined as 2 consecutive negative swab tests subsequent to DNA detection at the same site. Time to clearance was defined as the time elapsed from the date of the first positive HPV test result to the date of the first negative HPV test result after the last HPV detection.

[b] Persistent DNA detection was defined as detection of the same HPV type in any anogenital swab or biopsy specimen from the same site collected on >2 consecutive visits >6 months (±1 month) apart.

[c] Clearance was defined as 2 consecutive negative swab test results subsequent to persistent DNA detection at the same site. Time to clearance was defined as the time elapsed from the date of the first positive HPV test result to the date of the first negative HPV test result after the last HPV detection.

Duration and clearance of any HPV 6, 11, 16, or 18 DNA detection by anatomic site can be seen in Table 4.

Table 5 presents the risk factors for any detection of HPV 6, 11, 16, or 18 DNA in this population of heterosexual males who were seronegative and PCR negative for HPV 6, 11, 16, and 18 at enrollment. Higher lifetime number of sex partners, lack of condom use, and living in Africa (South Africa) were associated with a higher incidence of HPV detection. Interestingly, smoking and circumcision were not risk factors for HPV 6, 11, 16, or 18 infection.

Progression from incident HPV 6, 11, 16, or 18 DNA detection to cases of external genital warts was also analyzed (Figure 2). At 30 months after infection detection, roughly 30% of subjects with an HPV 6 or 11 DNA detection had a diagnosed

Table 4. Duration and Clearance of Any Detected Human Papillomavirus (HPV) Genotype 6, 11, 16, or 18, by Anatomic Site, Among Heterosexual Male Placebo Recipients Who Were Seronegative and Polymerase Chain Reaction Negative for All 4 HPV Types on Day 1

		Time to Clearance[a]							
Anatomic Site(s), HPV Type	Subjects, No.	Mo, Median	Mo, Mean	6 mo, Subjects, %	12 mo, Subjects, %	18 mo, Subjects, %	24 mo, Subjects, %	30 mo, Subjects, %	36 mo, Subjects, %
Penis									
HPV 6	115	6.7	8.4	45.2	35.7	10.4	7.0	0.0	1.7
HPV 11	44	6.0	7.2	50.0	36.4	11.4	0.0	2.3	0.0
HPV 16	153	8.9	10.8	34.0	31.4	17.7	9.2	5.2	2.6
HPV 18	86	7.5	9.1	38.4	40.7	9.3	7.0	4.7	0.0
Scrotum									
HPV 6	90	6.6	8.2	43.3	37.8	10.0	7.8	0.0	1.1
HPV 11	41	6.2	7.4	46.3	39.0	12.2	0.0	2.4	0.0
HPV 16	115	8.3	9.5	38.3	35.7	15.7	5.2	4.4	0.9
HPV 18	63	6.1	7.7	44.4	41.3	7.9	3.2	3.2	0.0
Perineum/anus									
HPV 6	66	6.1	7.7	48.5	28.8	18.2	3.0	1.5	0.0
HPV 11	25	3.9	6.9	52.0	32.0	8.0	4.0	4.0	0.0
HPV 16	70	6.1	8.1	45.7	32.9	15.7	4.3	1.4	0.0
HPV 18	36	6.1	7.7	36.1	52.8	8.3	2.8	0.0	0.0

Truncation occurred at the time disease was diagnosed.

[a] Clearance was defined as 2 consecutive negative swab test results subsequent to DNA detection at the same site. Time to clearance was defined as the time elapsed from the date of the first positive HPV test result to the date of the first negative HPV test result after the last HPV detection.

case of external genital warts. The incidence rate of external genital warts in subjects seronegative and PCR negative for HPV 6, 11, 16, and 18 on day 1 was 0.94 cases per 100 person-years at risk (data not shown).

DISCUSSION

In this report, we have shown that anogenital acquisition of HPV 6, 11, 16, and 18 is common among heterosexual males. Differences in HPV incidence were seen among both anatomic and geographic locations. In addition, the mean time to clearance among subjects with persistent HPV 6, 11, 16, or 18 DNA detection was comparable to that for subjects with any HPV 6, 11, 16, or 18 DNA detection. Most of the subjects in whom HPV DNA was detected did not have a clinically relevant lesion diagnosed, as shown by a cumulative external genital warts incidence of approximately 30% 30 months after any HPV 6 or 11 DNA detection, similar to that seen in the HPV Infection in Men (HIM) study [31].

The rate of any detection of HPV 6, 11, 16, or 18 DNA in the population aged 16–24 years was 9.0 cases per 100 person-years at risk. Data from a cohort study of the HIM [3] indicated HPV 6, 11, 16, and 18 incidence rates of 3.6, 0.9, 4.4, and 1.9 cases per 1000 person-months at risk, respectively. The corresponding rates from the current analysis, after conversion to person-month rates, were 3.2, 1.2, 3.7, and 2.1 cases per 1000 person-months at risk. While the rates of HPV detection in the current analysis correlate to those seen in the HIM study, it is important to consider that the overall rates reported in the current study are skewed by the high incidence seen in Africa (17.2 cases per 100 person-years at risk), a region with generally high HPV infection rates [32, 33]. No subjects in the HIM study were enrolled from Africa. In addition, the age of subjects enrolled in the HIM study ranged from 18–70 years, and this could have contributed to any differences seen.

Time to clearance in the current report can be more easily compared with the same data from the HIM study, as the same definition for clearance was used in both studies (2 consecutive negative test results after testing positive). Median time to clearance of HPV 6, 11, 16, and 18 in the HIM study was 6.4, 11.8, 12.2, and 6.3 months, respectively. This compares to median times to clearance of 6.1, 6.1, 7.7, and 6.3 months, respectively, for HPV 6, 11, 16, and 18 in the current study. A reason for the obvious difference in median times to clearance of HPV 16 in these 2 studies is not apparent, but it is possible that differences in study population, age distribution, sampling techniques, and HPV testing technologies might have played a role here. In addition, while the population of the current report was strictly heterosexual, this was not the case with the HIM study.

Comparing incidence data in the current report to similar data published by Insinga et al from females aged 16–23 years enrolled in a clinical trial of quadrivalent HPV vaccine yields interesting information [34]. The overall incidences of HPV 6, 11, 16, or 18 DNA detection among these subjects were 3.6, 0.4,

Table 5. Risk Factors for Any Detection of Human Papillomavirus Genotype 6, 11, 16, or 18 DNA Among Heterosexual Male Placebo Recipients

Risk Factor	Any HPV 6, 11, 16, or 18 DNA Detection (n = 415)	
	Percentage (No. of Infections/No. of Subjects)	Multivariate Relative Risk (95% CI)
Age, y		
15–20	25.2 (240/951)	1.0
21–27	23.1 (175/757)	0.90 (.73–1.12)
Tobacco use on day 1		
Never smoked	23.5 (227/966)	1.0
Current smoker	25.2 (28/111)	1.00 (.66–1.51)
Ex-smoker	25.4 (160/631)	0.90 (.73–1.12)
Sex history with female partners on day 1		
Age at first intercourse, y		
<15	29.7 (63/212)	1.0
15–19	24.4 (330/1354)	0.79 (.45–1.36)
≥20	15.8 (22/139)	0.78 (.58–1.04)
Sex partners, lifetime no.		
≤1	13.9 (58/416)	1.0
2	25.7 (93/362)	1.83 (1.32–2.56)
3–6	28.5 (264/927)	1.50 (1.06–2.14)
Frequency of lifetime condom use		
Never	14.1 (26/185)	1.0
Less than half of the time	26.1 (85/326)	1.48 (1.09–2.01)
More than half of the time	28.7 (160/557)	1.34 (.91–1.96)
Always	22.7 (144/635)	0.83 (.50–1.37)
New partners in last 6 mo, no.		
0	23.9 (241/1010)	1.0
1	24.0 (135/563)	1.01 (.79–1.28)
≥2	29.0 (38/131)	1.29 (.88–1.90)
Condom use frequency in the last 6 mo		
Never	23.3 (249/1067)	1.0
Always	26.1 (157/601)	0.74 (.55–1.00)
Sex history with female partners since last visit		
New partners, no.		
0	22.1 (251/1134)	1.0
1	30.7 (89/290)	1.12 (.87–1.44)
≥2	33.3 (66/198)	1.07 (.81–1.43)
Condom use frequency		
Never	27.4 (273/998)	1.24 (.98–1.56)
Always	24.7 (130/527)	1.0
Circumcision		
No	24.6 (271/1103)	1.0
Yes	23.8 (144/605)	1.0 (.76–1.31)
Region		
Africa	38.2 (102/267)	2.09 (1.51–2.90)
Asia-Pacific	10.2 (14/137)	0.42 (.22–.79)
Europe	22.6 (42/186)	0.50 (.32–.77)
Latin America	23.9 (172/720)	0.81 (.58–1.14)
North America	21.4 (85/398)	1.0

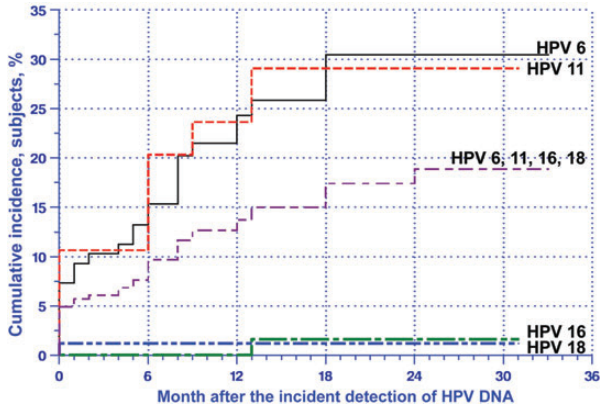

Figure 2. Kaplan-Meier analysis of the progression from incident detection of human papillomavirus (HPV) DNA to an incident, clinically relevant, type-related external genital warts among heterosexual male subjects in the placebo arm.

5.4, and 2.1 cases per 100 person-years at risk, respectively; data very similar to the data presented currently. The median durations of HPV 6, 11, 16, and 18 DNA detection (censoring at disease or clearance) among females aged 16–23 years were 6.2, 6.5, 11.7, and 12.4 months, respectively. While very similar for HPV types 6 and 11, the median duration of infection was higher among females 16–23 years of age than among the males in the current report (7.7 months for HPV 16 and 6.2 months for HPV 18). The reason for the discrepancy seen could lie in one of several factors, most notably the physiological differences between male and female anatomy. Only external anogenital swab specimens were taken in the current study.

In conclusion, we have shown that the acquisition of HPV 6, 11, 16, or 18 is common among males. We have also shown differences in HPV DNA detection rates at different anogenital anatomic sites. While many of these infections clear, the median time to clearance is likely to be ≥6 months, making HPV transmission likely. Therefore, male vaccination may reduce the transmission and overall incidence of HPV infections, as well as the rate of HPV-associated diseases among heterosexual men in the community.

Notes

Acknowledgments. We thank study participants and investigators.

Financial support. This work was supported by Merck & Co., Inc. Whitehouse Station, NJ.

Potential conflicts of interest. D. F. has received funding for consultancy and board membership and has grants or pending grants through his institution from Merck. A. G. has received funding through her institution for consultancy and lectures and has grants or grants pending from Merck. S. G. has received grants, consulting fees, support for travel to meetings, and support for speaking engagements from Merck and has received support for consultancy, has received donated equipment for testing, and has grants or grants pending from Covidien. R. J. H. has received salary from WSLHD and payment for lectures from Gilead. H. M. has received funding through his institution for travel to board meetings and has received

honoraria for board meetings from Merck. E. M. has received grants through his institution for conducting HPV vaccine trials, consulting fees, support for travel, fees for board membership, and fees for lectures from Merck. J. P. has received grants through his institution and travel support from Merck, has received fees for board membership from Pharmajet, has received fees for consultancy from Qiagen, has received fees for lectures from Hologic, owns Aura Biosciences stock or stock options, collects royalties from UpToDate, and has grants or grants pending from Merck and Hologic. M. S. has received consulting fees, support for travel to meetings, and fees for board membership from Merck. D. G., R. M. H., S. V., and J. B. M. are employees of Merck and may own stock and/or stock options.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Cates W Jr. Estimates of the incidence and prevalence of sexually transmitted diseases in the United States. American Social Health Association Panel. Sex Transm Dis **1999**; 26(4 Suppl):S2–7.
2. International Agency for Research on Cancer Working Group. Human papillomaviruses. Lyon, France: IARC, **2007**.
3. Giuliano AR, Lee JH, Fulp W, et al. Incidence and clearance of genital human papillomavirus infection in men (HIM): a cohort study. Lancet **2011**; 377:932–40.
4. Syrjanen S. Human papillomavirus (HPV) in head and neck cancer. J Clin Virol **2005**; 32:S59–66.
5. Gillison ML, Lowy DR. A causal role for human papillomavirus in head and neck cancer. Lancet **2006**; 363:1488–9.
6. Giuliani L, Favalli C, Syrjanen K, Ciotti M. Human papillomavirus infections in lung cancer. Detection of E6 and E7 transcripts and review of the literature. Anticancer Res **2007**; 27:2697–704.
7. Syrjänen KJ. HPV infections and oesophageal cancer. J Clin Pathol **2002**; 55:721–8.
8. Giuliano AR, Lazcano E, Villa LL, et al. Circumcision and sexual behavior: factors independently associated with human papillomavirus detection among men in the HIM study. Int J Cancer **2009**; 124:1251–7.
9. Giuliano AR, Lu B, Nielson CM, et al. Age-specific prevalence, incidence, and duration of human papillomavirus infections in a cohort of 290 US men. J Infect Dis **2008**; 198:827–35.
10. Partridge JM, Hughes JP, Feng Q, et al. Genital human papillomavirus infection in men: incidence and risk factors in a cohort of university students. J Infect Dis **2007**; 196:1128–36.
11. Burchell AN, Winer RL, de Sanjose S, Franco EL. Chapter 6: Epidemiology and transmission dynamics of genital HPV infection. Vaccine **2006**; 24(Suppl 3):S52–61.
12. Burchell AN, Coutlee F, Tellier PP, Hanley J, Franco EL. Genital transmission of human papillomavirus in recently formed heterosexual couples. J Infect Dis **2011**; 204:1723–9.
13. Insinga R, Dasbach E, Elbasha E, Liaw K, Guris D. Outcomes following incident HPV 6/11/16/18 DNA detection in young men. Presented at: 25th International Papillomavirus Conference, Malmo Sweden, 8 May 2009.
14. Smith JS, Melendy A, Rana RK, Pimenta JM. Age-specific prevalence of infection with human papillomavirus in females: a global review. J Adolesc Health **2008**; 43(4 Suppl):S5–25, S25.
15. Smith JS, Gilbert PA, Melendy A, Rana RK, Pimenta JM. Age-specific prevalence of human papillomavirus infection in males: a global review. J Adolesc Health **2011**; 48:540–52.
16. Kjaer SK, Munk C, Winther JF, Jorgensen HO, Meijer CJ, van den Brule AJ. Acquisition and persistence of human papillomavirus infection in younger men: a prospective follow-up study among Danish soldiers. Cancer Epidemiol Biomarkers Prev **2005**; 14:1528–33.
17. Lajous M, Mueller N, Cruz-Valdez A, et al. Determinants of prevalence, acquisition, and persistence of human papillomavirus in healthy Mexican military men. Cancer Epidemiol Biomarkers Prev **2005**; 14:1710–6.
18. van Doornum GJJ, Hooykaas C, Juffermans LHJ, et al. Prevalence of human papillomavirus infections among heterosexual men and women with multiple sexual partners. J Med Virol **1992**; 37:13–21.
19. van Doornum GJ, Prins M, Juffermans LH, et al. Regional distribution and incidence of human papillomavirus infections among heterosexual men and women with multiple sexual partners: a prospective study. Genitourin Med **1994**; 70:240–6.
20. Wikström A, Popesca C, Forslund O. Asymptomatic penile HPV infection: a prospective study. Int J STD AIDS **2000**; 11:80–4.
21. Svare EI, Kjaer SK, Worm AM, Østerlind A, Meijer CJLM, van den Brule AJC. Risk factors for genital HPV DNA in men resemble those found in women: a study of male attendees at a Danish STD clinic. Sex Transm Infect **2002**; 78:215–8.
22. Vaccarella S, Franceschi S, Herrero R, et al. Sexual behavior, condom use, and human papillomavirus: pooled analysis of the IARC human papillomavirus prevalence surveys. Cancer Epidemiol Biomarkers Prev **2006**; 15:326–33.
23. Shin HR, Lee DH, Herrero R, et al. Prevalence of human papillomavirus infection in women in Busan, South Korea. Int J Cancer **2003**; 103:413–21.
24. Castellsagué X, Ghaffari A, Daniel RW, Bosch FX, Muñoz N, Shah KV. Prevalence of penile human papillomavirus DNA in husbands of women with and without cervical neoplasia: a study in Spain and Colombia. J Infect Dis **1997**; 176:353–61.
25. Baldwin SB, Wallace DR, Papenfuss MR, et al. Human papillomavirus infection in men attending a sexually transmitted disease clinic. J Infect Dis **2003**; 187:1064–70.
26. Weaver BA, Feng Q, Holmes KK, et al. Evaluation of genital sites and sampling techniques for detection of human papillomavirus DNA in men. J Infect Dis **2004**; 189:677–85.
27. Giuliano AR, Palefsky JM, Goldstone S, et al. Efficacy of quadrivalent HPV vaccine against HPV Infection and disease in males. N Engl J Med **2011**; 364:401–11.
28. Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med **2007**; 356:1928–43.
29. Iftner T, Germ L, Swoyer R, et al. Study comparing human papillomavirus (HPV) real-time multiplex PCR and Hybrid Capture II INNO-LiPA v2 HPV genotyping PCR assays. J Clin Microbiol **2009**; 47: 2106–13.
30. The FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med **2007**; 356:1915–27.
31. Anic GM, Lee JH, Stockwell H, et al. Incidence and human papillomavirus (HPV) type distribution of genital warts in a multinational cohort of men: the HPV in men study. J Infect Dis **2011**; 204: 1886–92.
32. Tarnaud C, Lissouba P, Cutler E, Puren A, Taljaard D, Auvert B. Association of low-risk human papillomavirus infection with male circumcision in young men: results from a longitudinal study conducted in Orange Farm (South Africa). Infect Dis Obstet Gynecol **2011**; 2011:567408.
33. Backes DM, Bleeker MC, Meijer CJ, et al. Male circumcision is associated with a lower prevalence of human papillomavirus-associated penile lesions among Kenyan men. Int J Cancer **2012**; 130:1888–97.
34. Insinga RP, Dasbach EJ, Elbasha EH, Liaw KL, Barr E. Incidence and duration of cervical human papillomavirus 6, 11, 16, and 18 infections in young women: an evaluation from multiple analytic perspectives. Cancer Epidemiol Biomarkers Prev **2007**; 16:709–15.