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Difficulties in estimating the male-to-female sexual transmissibility of human papillomavirus infection

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Estimates of transmissibility of infectious agents such as human papillomavirus (HPV) are important for developing preventive measures and determining the impact of such interventions. Based on the results of epidemiologic studies, HPV appears to be highly transmissible;^{1–8} however, empirical data on HPV transmissibility are lacking.^{9–11} We sought to design and conduct a study among couples to provide the first empirical estimate of male-to-female sexual transmissibility of HPV. However, we faced several difficulties in achieving this goal. Here we present the design and descriptive results of this study in brief and these difficulties in detail.

Information on study population arose from a larger study described in detail elsewhere.⁵ Briefly, between December 2000 and November 2006, 244 women (age range: 18–22) were recruited to a longitudinal study of HPV infection through invitational letters mailed to 24,201 female University of Washington undergraduates and informational flyers at the student health clinic. Participants were eligible to enroll if they had never had vaginal intercourse with a male partner (i.e., virgin) or had first had intercourse with one male partner within the previous three months (i.e., peri-virgin). Consenting women were asked to refer their first male partner to the study and were given a letter of recruitment to forward to him.

Every two weeks, women completed a Web-based diary designed to capture daily sexual behavior information such as date and number of acts of intercourse with a new partner.^{5, 12} Women were followed-up with gynecological examinations every four months. At each visit, self-collected vaginal swabs and clinician-collected cervical and vulvovaginal swabs were collected. Men were seen only for one visit. They underwent a clinician-administered interview about their medical and sexual history and a genital examination including specimen collection from the penis, urethra, and scrotal area, described in detail elsewhere.¹³ All samples were tested for HPV DNA by polymerase chain reaction (PCR)-based methods. Specimens testing positive by a generic probe were typed using a reverse line-blot assay (Roche Molecular Systems) for 37 distinct HPV types.¹⁴ PCR results of vaginal, cervical, and vulvovaginal swabs for women and penile, urethral, and scrotal swabs for men were combined to determine genital HPV status in each participant. Institutional Review Board of the University of Washington approved the study; informed consent was obtained from all participants.

Male partners were enrolled for 33 women. Information on 19 couples was excluded due to the following reasons: one woman did not report any sexual activity in the diary; three men were not the first sex partner of their female partner; and 15 couples were not found to be infected with HPV. Of the remaining 14 couples, both partners were found to be infected with HPV in five couples and the male partner only was found to be infected in three couples. Descriptive results for these eight couples and for the other six couples in whom, unexpectedly, the female partner was found to be infected with HPV, while the male partner was not, are provided in Tables 1 and 2.

Investigators who embark upon designing a methodologically sound study to find empirical estimates of male-to-female sexual transmissibility of HPV may face the following difficulties:

Recruitment of peri-virgin women

Recruitment of adolescent females who may not engage in sexual activity for some years is not feasible due to the required long follow-up time and to ethical considerations. Recruitment of women who have already been engaged in sexual activity for some years is also problematic. First, such women may have already been infected with some types of HPV prior to enrollment, thereby reducing or eliminating their susceptibility to infection with those types during the observation period. It is not possible to determine with a reasonable degree of certainty whether a sexually active woman is susceptible to infection with specific HPV types. Although the immune response appears to be highly effective in preventing re-infection with the same HPV type,¹⁵ less than two-thirds of women with molecular evidence of HPV infection mount a measurable serological response.¹⁶ Second, it is likely that accurate and detailed information on sexual behavior during the period when such women were sexually active but not enrolled in the study as well as the infection status of the earlier partners would be difficult to obtain.

Recruitment of the first male sex partner

The first relationship may be unstable and short; thus, women may not be willing or able to refer their first male sex partner to the study, or the first male partner himself may not be willing to participate in the study. We took advantage of a university setting where relationships are frequently formed among college students; both female students and their first male partners may be willing to enroll in a study conducted at a clinic located on campus. Nonetheless, while we had originally planned to enroll 50–100 male partners, only 33 were enrolled, out of whom three were not the first male partner, resulting in a diminished power for our study.

The time interval between the dates of the couple's first intercourse and the male partner's visit

Ideally, this time interval should be as short as possible to reflect the HPV status of the male partner at the time of intercourse with the female partner. We categorize couples in this study in whom the female partner was infected with an HPV type that was not detected in her male partner into two groups. In the first group, the date of the male's visit was *after* the date of detection of infection in the female partner. The male partner may have cleared/suppressed his infection to an undetectable level by the time he was tested. This is likely as the duration of HPV infection among men is believed to be shorter than that among women.¹⁷ In the second group, the date of the male's visit was *before* the date of detection of infection in the female partner. The male partner may have acquired his infection after his visit (e.g., through sexual contact with another female partner). Testing men in a

longitudinal (rather than cross-sectional) fashion would have enabled us to clarify some of these uncertainties.

Accuracy of self-reports

While we made efforts to measure the sexual behavior as accurate and detailed as possible through a Web-based diary, some degrees of misclassification, resulting in a lack of concordance, cannot be ruled out. For instance, women who were infected with HPV types not detected in their male partner may have failed to report a sexual contact with another male partner. Additionally, one female partner in this study was found to be infected with HPV while she was a virgin. It is possible that she simply did not report the date of her first intercourse accurately.

Nonsexual and noncoital sexual transmission

HPV can be transmitted through noncoital sexual (e.g., digital-genital contact) as well as nonsexual modes.^{18, 19} For instance, it has been shown that HPV DNA can be detected in finger and fingernail samples of men.²⁰ This may provide an alternative explanation for detection of HPV infection among virgin female partners. Future studies on HPV transmission may address this possibility by sampling nongenital sites from participants.

Genital sampling methods and sensitivity of HPV testing

While we collected samples from multiple genital sites and used highly sensitive PCR methods for detection of HPV infection, it is possible that some HPV infections were missed, especially among the male partners. The technical limitations of HPV detection and lower quantity of HPV viral load in the male genital samples compared with that in the female genital samples have been discussed elsewhere.^{17, 21} Furthermore, the possibility of laboratory errors and sample contamination in couples in whom the female partner was found to be infected with HPV but the male partner was not cannot be ruled out. Finally, even when the HPV DNA is detected in the male partner, its presence alone may not be sufficient to constitute infectiousness to his partner.

The lag period between the time of infection acquisition and infection detectability

The shortest observed duration of the lag period between the time of infection acquisition and infection detectability among the couples in this study was 18 days. Biologically, epithelial cells need to mature and differentiate providing cellular events required for HPV replication and consequently detection.²² Any analytical method for estimating HPV transmissibility should take this lag period into account.

Interval censoring

HPV infection status is usually assessed periodically (e.g., every four months in this study), leading to interval censoring. The exact time of transmission and number of acts of intercourse necessary for transmission are unknown. Frequent testing with shorter intervals can provide valuable information towards clarifying these unknowns.

We hope that this report can encourage our colleagues to improve our methodology or develop alternative novel approaches to provide empirical estimates of HPV transmissibility. We expect to describe efforts in resolving some of the aforementioned difficulties and provide empirical estimates of the male-to-female sexual transmissibility of HPV in a future report.

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Table 1

Characteristics of eight couples in whom at least one type of HPV was detected in the single visit of the first male partner

Couple	Infection in male		Infection in female		Date started diary	Average no. of intercourse per week [†]	% condom use [‡]	Date of censoring [#]
	Type	Date of detection	Type	Date of detection				
1	33, 40, 45, 82	202	33, 39, 82, 40, 45	252 365	-23	6.8 5.9	9.8 9.0	365
2	16, 51	145	16 51	124 256	-12	3.1 3.0	18.2 20.0	256
3	18, 39, 54, 66	490	18, 39, 42, 54, 66	318	14	7.5	100	318
4	51, 54, 62, CP6108	23	54	18	2	0.4	100	18
5	58	90	51	358	48	2.8	72.0	456
6	11	253	None	NA [¶]	91	1.6	81.0	1191
7	3	14	None	NA	-126	1.9	3.6	101
8	16, 18, 84	109	None	NA	74	2.7	100	91

Note. The reference day for all dates is the date of first intercourse; negative numbers indicate number of days before the day of first intercourse and positive numbers indicate number of days after the day of first intercourse.

[¶]Not applicable.

[†]During the period of time between the first intercourse in the diary and infection detection or date of censoring, whichever came first.

[‡]During the period of time between the first intercourse in the diary and infection detection or date of censoring, whichever came first.

[#]The visit when all HPV types which had been detected in the male partner were also detected at least once in the female partner, the visit after which the female partner acquired a new (i.e., second) male partner, or her last visit in the study, whichever came first.

Table 2

Characteristics of six couples in whom at least one type of HPV was detected in the female partner but not in the male partner

Couple	Date of male's visit	Infection in female		Date started diary	Average no. of intercourse per week [†]	% condom use [‡]
		Type	Date of detection			
9	116	54, 56	107	-7	5.9	81.0
10	20	16, 52, 59	70	-359	1.8	94.0
		55	203		1.2	60.0
		CP6108	344		1.4	30.0
11	12	53	-177	-873	NA [¶]	NA
12	64	67	781	36	0.4	35.0
13	256	18, 84	678	17	2.9	5.0
14	446	81	68	51	2.8	100

Note. The reference day for all dates is the date of first intercourse; negative numbers indicate number of days before the day of first intercourse and positive numbers indicate number of days after the day of first intercourse.

[¶]Not applicable; the date of intercourse was after the date of HPV detection.

[†]During the period of time between the first intercourse in the diary and infection detection or date of censoring, whichever came first.

[‡]During the period of time between the first intercourse in the diary and infection detection or date of censoring, whichever came first.