Hand-to-genital and genital-to-genital transmission of human papillomaviruses between male and female sexual partners (HITCH): a prospective cohort study

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Summary

Background Hand-to-genital contact is hypothesised to be a transmission mode of human papillomavirus (HPV) of the Alphapapillomavirus genus. We compared the relative importance of hand-to-genital and genital-to-genital HPV transmission between sexual partners.

Methods In this prospective cohort study, we recruited and followed up female university students aged 18–24 years and their male sexual partners in Montreal, QC, Canada (2005–11). Participants were eligible if they had initiated sexual activity within the past 6 months. Women were examined at clinic visits at baseline and every 4–6 months for up to 24 months. Men had a baseline visit and a single follow-up visit approximately 4 months later. Partners provided hand and genital swab samples, which we tested for DNA of 36 HPV types using PCR. We assessed predictors of incident type-specific HPV detections using Cox proportional hazards models.

Findings Participants were recruited between June 5, 2006, and April 4, 2013. 264 women and 291 men had valid hand samples. The hazard ratio (HR) of incident detection of HPV in genital samples from women was 5·0 (95% CI 1·5–16·4) when her partner was positive for the same HPV type on his hand versus negative, but adjustment for his genital HPV status reduced the HR to 0·5 (0·1–1·8). Similarly, the HR of incident detection of HPV on men's genitals was 17·4 (95% CI 7·9–38·5) when his partner was positive for the same HPV type on her hand versus negative, but adjustment for her genital HPV status reduced the HR to 2·3 (0·9–6·2). Conversely, the HR of type-specific incident detection of HPV in genital samples associated with partner genital HPV positivity was 19·3 (95% CI 11·8–31·8) for women and 28·4 (15·4–52·1) for men after adjustment for their hand HPV status.

Interpretation Clinicians can reassure their patients that HPV transmission is unlikely to occur through hand-to-genital contact. The majority of genital HPV infections are likely to be caused by genital-to-genital sexual transmission.

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Introduction

Human papillomavirus (HPV) types of the genus Alphapapillomavirus (alpha-HPV) are sexually transmitted infections, many of which cause anogenital and oropharyngeal cancers in men and women.[1] Alpha-HPV types mainly infect mucosal tissues.[2] Because HPV prevalence is highly correlated with the number of recent and lifetime genital sex partners, a large body of evidence suggests that alpha-HPV types are mainly transmitted through genital-to-genital contact.[3] Over the years, some researchers have also speculated as to the possibility of hand-to-genital transmission of alpha-HPV types.[4–8] This hypothesis is supported by the frequent detection of alpha-HPV DNA on hands and under fingernails,[8–10] and the high concordance between hand and genital HPV types in the same person[6,9] and between partners.[8] However, there has been scepticism as to the importance of hand-to-genital transmission of alpha-HPV types.[11] The high correlation between hand and genital HPV detection makes it difficult to separate cause from effect and to establish the direction of transmission. To what extent HPV transmission events occur from hand-to-genital or genital-to-hand contact is unclear.

The general public is becoming more aware of HPV because of the availability of vaccines and cervical cancer screening with HPV tests, and many people might have questions and anxieties regarding the transmission and risk of HPV infections.[12,13] Clinicians and public health workers should be able to inform the public on the modes and risks of transmission of HPV. Elucidating the importance of hand-to-genital transmission and providing public health messages on the basis of strong scientific evidence is therefore important. This information could assuage fears of inadvertently transmitting HPV to partners or of becoming infected from hand-to-genital contacts.

Our objective was to establish whether hand-to-genital transmission of HPV is supported by examining

Research in context

Evidence before this study

While hand-to-genital transmission has long been hypothesised as a mode of human papillomavirus (HPV) transmission, little data have been published on the prevalence and incidence of HPV on hands to test this hypothesis. We did a literature review for studies published in English on March 23, 2018, by searching PubMed with the search terms "papillomavirus infections/transmission", "papillomavirus infections", "alphapapillomavirus", or "HPV" and "hand/virology", "fingers/virology", or "disease transmission, infectious", and with the terms "hand", "HPV", and "transmission". The inclusion criteria were studies that evaluated alphapapillomavirus concordance between hand and genital sites, either within an individual or between sex partners, and studies assessing the incidence of transmission from hand to genitals or from genitals to hand. We identified five studies that examined alphapapillomavirus type concordance between hand and genital sites or incidence of transmission between sites in the past 20 years. The conclusions from these studies have been conflicting, with some concluding that hand-to-genital transmission is possible, others concluding it is unlikely, and others concluding it is unclear. The main limitations of previous studies have been a small sample size and the scarcity of data on sexual partners to assess sexual transmission.

Added value of this study

This study on sex partners with genital and hand HPV data is the largest to date. We controlled for confounding due to the correlation in HPV positivity at multiple sites to assess the direction of HPV transmission between sites and between partners. Our results provide the strongest evidence to date that genital HPV acquisition is unlikely to be due to hand-to-genital transmission, occurs mostly as a result of genital-to-genital contact, and that most HPV DNA on the hands is likely to be present from self-inoculation from the genitals.

Implications of all the available evidence

Because of the carcinogenicity of many HPV types, cervical cancer screening is increasingly done using HPV testing. Many women will become aware that they are HPV positive and have questions regarding how they contracted HPV, and the risk of transmission to their partners. Our results suggest that clinicians can reassure their patients that transmission is unlikely to occur through hand contact.

cross-sectional and prospective hand and genital HPV incidence in couples, or whether the detection of HPV DNA in the hand is merely carriage that is incidental to genital infections.

Methods

Study design, participants, and data collection

We used data from the HPV Infection and Transmission Among Couples through Heterosexual Activity (HITCH) study, which examined the transmission of HPV in young, heterosexual, newly formed couples. Study procedures have been previously described elsewhere.[14–17] Briefly, HITCH was a prospective cohort study that enrolled female university and college students aged 18–24 years and their male partners aged at least 18 years from four universities and 13 colleges in Montréal, Canada, during 2005–11 (with some women recruiting new male partners up until 2013). Participants were recruited through promotional materials distributed on campus and student venues. Eligible couples needed to have initiated sexual activity within the past 6 months. Women were excluded if they were pregnant or planning to become pregnant within the next 2 years, if they had a hysterectomy, or if they had a history of cervical lesions or cancer. The ethical review committees of McGill University, Concordia University, and the Centre Hospitalier de l'Université de Montreal approved the study. All participants provided written informed consent.

Women were examined at clinic visits at baseline and every 4–6 months for up to 24 months. Men had a baseline visit and a single follow-up visit approximately 4 months later. Participants answered self-administered behavioural questionnaires and provided biological samples for HPV testing at each study visit. Initially, only genital samples were collected, but beginning in 2008 we started collecting hand samples during the first two visits (at enrolment and at 4 months) when both men and women were scheduled to attend a clinic. If a couple ended their relationship during the study, the participants were encouraged to enrol any new eligible partner, although this enrolment was not required for continued participation. These participants provided additional hand samples corresponding with the first two visits of their newly recruited partner, which were included in analyses. Most hand samples came from couples recruited after 2008; however, exceptionally some hand samples were taken from individuals who were recruited previously and who recruited new partners into the study after 2008, or whose second visit occurred following the start of hand sample collection.

Participants were instructed to wash their hands with soap and water before hand sampling. An ultrafine emery paper was used to exfoliate the palmar surface of the index and middle fingers before sampling with a Dacron swab. Wearing latex gloves, the study nurse used a cytobrush to swab the fingertips and under the nails of the dominant hand. Women self collected vaginal specimens using a Dacron swab, after being instructed by the study nurse. For men, the nurse collected epithelial cells from the penis and scrotum in separate sample containers using gentle exfoliation with ultrafine emery paper followed by swabbing with a Dacron swab. The Dacron swabs were placed into vials with Preservcyt

(Hologic, Marlborough, MA, USA), agitated to release cells, and then discarded; the emery papers were also placed in the respective vials. Samples were processed and DNA extracted as previously described.[17]

HPV DNA testing

Genital and hand specimens were tested by PCR using the Linear Array HPV genotyping assay (Roche Molecular Systems, Alameda, CA, USA).[18] This technique detects DNA from 36 mucosal HPV genotypes of the alpha-papillomavirus genus (6, 11, 16, 18, 26, 31, 33, 34, 35, 39, 40, 42, 44, 45, 51, 52, 53, 54, 56, 58, 59, 61, 62, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82 [including its subtype IS39], 83, 84, and 89). β-globin DNA was co-amplified to assess DNA integrity of samples and to control for the presence of cells. A sample was considered valid if β-globin DNA was detected. An individual was considered to be positive for hand type-specific HPV if either the fingernail or finger samples were positive for a given HPV type. A man was considered to be positive to genital type-specific HPV if either the penile or scrotal samples were positive for a given HPV type.

Statistical analysis

We restricted analyses to clinic visits in which participants had valid hand samples. The unit of analysis was type-specific HPV positivity in the hand or genital samples at each clinic visit. Each participant therefore contributed multiple observations to each analysis with 36 different HPV types and with multiple clinic visits.

For the analyses of prevalence of HPV, we calculated the observed:expected ratio of the probability of detecting the same HPV type in participants' hand and genital samples during a given visit, summed over all 36 HPV types:

Observed:expected ratios higher than 1 indicate a type-specific co-detection pattern that occurs more often than would be expected if the probability of HPV infection were completely independent between hand and genitals, whereas ratios of less than 1 indicate a type-specific co-detection pattern that occurs less often than would be expected if HPV were distributed completely independently across hands and genitals. The 95% CIs were generated using block bootstrapping with 1000 resamples of participants.[19]

We used multilevel logistic regression models to assess whether type-specific hand and genital HPV positivity was associated with same-type positivity at other sites during the same visit. Multilevel models included a random intercept for each participant. This model accounts for potentially correlated data due to repeated measurements on the same person (multiple HPV types and multiple clinic visits). For partner-level analyses, we further restricted the analyses to study visits in which couples both had valid samples taken on the same day. In a separate analysis, we analysed whether the questionnaire-reported frequency of hand-genital and vaginal sex were associated with the hand-genital concordance between partners. We established the mean of men and women's answers regarding their reported frequency of hand-genital and vaginal sex from their questionnaires.

We plotted the cumulative risks of incident HPV acquisition using Kaplan-Meier curves. We assessed

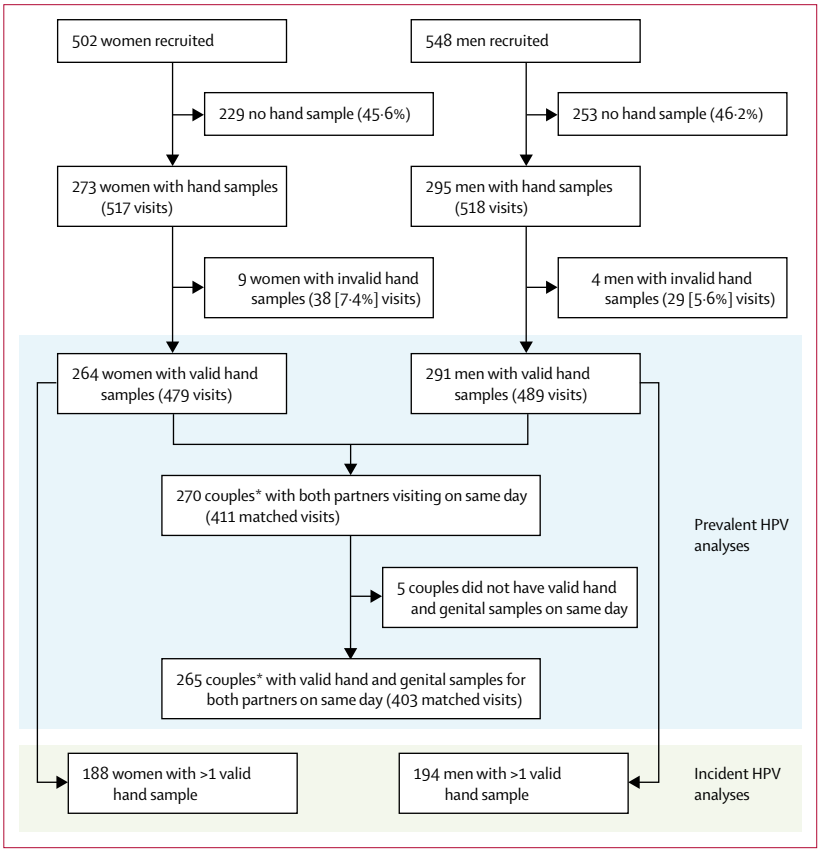

Figure 1: **HITCH study participants**
Hand sampling began half way through study recruitment in 2008. Invalid hand and genital samples had no detected β-globin DNA. HPV=human papillomavirus. *There are more couples than women in cross-sectional partnered analyses because some women recruited multiple male partners in the study and were part of more than one couple.

	Total HPV type detections*			HPV prevalence†	
	Hand	Genital	Either hand or genital	Hand (women N=479; men N=489)	Genital (women N=473; men N=483)
Any HPV type in women	300	748	805	170 (35%)	283 (60%)
Any HPV type in men	352	903	959	178 (36%)	306 (63%)
High-risk HPV types‡ in women	126	326	344	95 (20%)	203 (43%)
High-risk HPV types‡ in men	143	356	384	105 (21%)	218 (45%)
Low-risk HPV types‡ in women	126	291	317	99 (21%)	186 (39%)
Low-risk HPV types‡ in men	135	386	399	101 (21%)	226 (47%)

HPV=human papillomavirus. *Number of type-specific detections at all visits. Each individual can contribute multiple HPV type detections if samples are positive for multiple types. †Proportion of samples that are positive for any of the group's HPV types across visits. Denominators are the number of valid hand and genital samples over all visits. ‡High-risk HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68, and low-risk HPV types 6, 11, 40, 42, 44, 54, 61, 62, 71, 72, 81, 83, 84, and 89.

Table 1: **HPV DNA type-specific number of detections and prevalence in valid hand samples and concomitant genital samples**

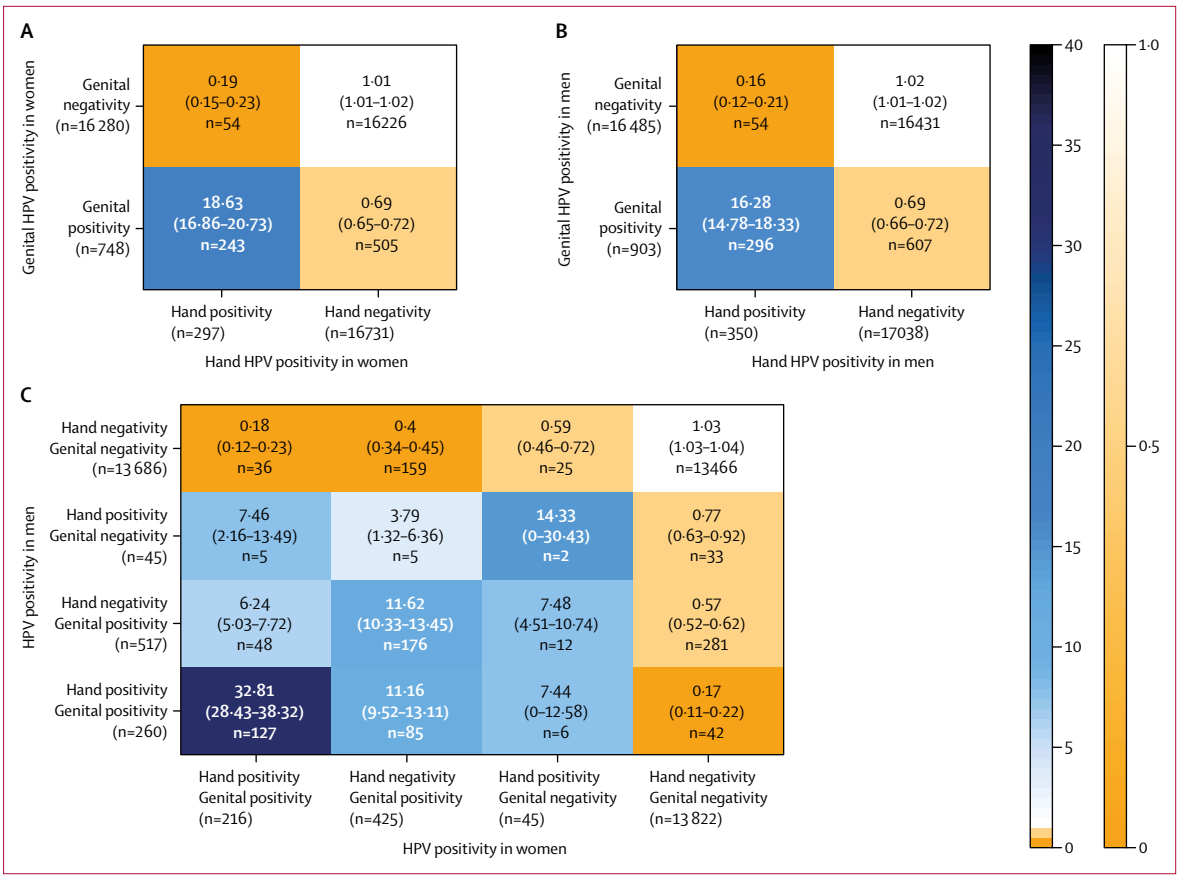

Figure 2: **Observed:expected ratios of HPV type-specific detection patterns by site pooled over all HPV types**
The data are presented for women (A), men (B), and couples (C). Analyses are restricted to visits with concurrently valid hand and genital samples (473 for women, 483 for men, and 403 for couples). Marginal totals (the denominators) are derived from the number of visits with concurrent valid hand and genital samples multiplied by the 36 HPV types. Marginal totals are lower in couples than in men and women individually because partnership analyses are restricted to the visits in which both partners had valid hand and genital samples taken on the same day. The vertical graded colour bar indicates the magnitude of the observed:expected ratios. Numbers in parentheses represent the 95% percentiles of 1000 block bootstrap resamples. HPV=human papillomavirus.

whether incident hand and genital HPV detections were associated with HPV positivity at other self and partner sites at the preceding visit using Cox proportional hazards models with a random effect for each participant (log-normal frailty model) and Efron's approximate likelihood.[20,21] We restricted prospective analyses to individuals with at least two visits with valid hand samples, who were type-specific HPV negative at the baseline visit at the analysed site, and who had valid HPV data at the baseline visit for the other self and partner sample sites. Because HPV infections are asymptomatic, we imputed incident HPV acquisitions as occurring midway through the interval when the individual became HPV positive. Participants who had no incident type-specific HPV detection were censored at their last study visit with a valid hand sample. In sensitivity analyses, we fitted a fixed effects Cox model using interval-censoring methods to assess whether midpoint imputation affected the results.

Because of the infectious nature of HPV, positivity at different sites is expected to be highly correlated. To control for confounding, we included type-specific HPV positivity at all other exposure sites as predictors in multivariable logistic and Cox regression models. The objective was to establish which sites were the strongest predictors of type-specific HPV detection at the outcome site, unconfounded by same-type HPV positivity at other sites. Statistical analyses were done using SAS 9.4 and R 3.5.1.

Role of the funding source

The study sponsors had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Participants were recruited between June 5, 2006, and April 4, 2013. 264 women during 479 visits and 291 men (37 recruited after baseline) during 489 visits provided at least one valid hand HPV DNA sample (figure 1).

	HPV type-specific positivity probability (if the exposure site is positive)*†	HPV type-specific positivity probability (if exposure site is negative)†‡	Univariate odds ratio (95% CI)	Odds ratio adjusted for all sites (95% CI)§
Women				
Hand HPV positivity by exposure site				
Genital (own)	243/748 (32%)	54/16 280 (<1%)	170·1 (121·0–239·0)	49·5 (30·6–80·2)
Genital (partner)	194/792 (24%)	68/13 860 (<1%)	74·3 (53·9–102·5)	3·0 (1·8–4·9)
Hand (partner)	141/312 (45%)	121/14 484 (<1%)	127·0 (88·8–181·7)	6·7 (4·2–10·4)
Genital HPV positivity by exposure site				
Hand (own)	243/297 (82%)	505/16 731 (3%)	189·4 (131·7–272·5)	50·7 (30·5–84·3)
Genital (partner)	436/777 (56%)	205/13 731 (1%)	96·4 (76·4–121·5)	44·5 (34·1–58·0)
Hand (partner)	222/306 (73%)	423/14 346 (3%)	105·6 (76·5–145·8)	4·1 (2·7–6·3)
Men				
Hand HPV positivity by exposure site				
Genital (own)	296/903 (33%)	54/16 485 (<1%)	189·3 (133·3–268·7)	54·4 (34·5–85·9)
Genital (partner)	222/645 (34%)	84/14 007 (<1%)	104·7 (76·1–144·2)	5·1 (3·3–7·8)
Hand (partner)	141/262 (54%)	171/14 534 (1%)	133·5 (92·0–193·7)	7·3 (4·7–11·4)
Genital HPV positivity by exposure site				
Hand (own)	296/350 (85%)	607/17 038 (4%)	205·0 (142·0–296·1)	51·8 (32·1–83·6)
Genital (partner)	436/641 (68%)	341/13 867 (2%)	102·4 (80·5–130·3)	46·7 (35·4–61·5)
Hand (partner)	194/262 (74%)	598/14 390 (4%)	82·0 (57·9–116·1)	2·5 (1·5–4·1)

The data are n/N (%) or odds ratio (95% CI). HPV=human papillomavirus. *Probability that the outcome site is HPV DNA type-specific positive if the exposure site is same-type positive. †The denominators are 36 HPV types multiplied by the number of visits in which both the exposure and the outcome site samples were valid and taken on the same day. Numbers might be higher than in figure 2C, which is restricted to visits with complete data in which both partners had valid hand and genital samples taken on the same day, a more stringent criterion (ie, four concurrent valid samples instead of two). ‡Probability that the outcome site is HPV DNA type-specific positive if the exposure site is same-type negative. §Hand positivity: mutually adjusted for genital (own), genital (partner), and hand (partner) exposure site positivity; genital positivity: mutually adjusted for hand (own), genital (partner), and hand (partner) exposure site positivity.

Table 2: **Probability and odds ratios of hand and genital HPV DNA positivity stratified by HPV positivity at other sites at the same visit, pooled over all HPV types**

Concomitant genital DNA samples were valid in 473 (99%) of 479 female visits and 483 (99%) of 489 male visits. The participants included in the present analyses had a mean age of 21·0 years (SD 2·3 years) for women and 23·2 years (SD 3·9 years) for men and reported a median of four (IQR 3–6) vaginal sex acts per week (appendix).

188 women and 194 men had more than one study visit with a valid hand sample and were included in prospective analyses. The median number of visits was two (IQR 1–2) for women and two (IQR 1–2) for men. Women were followed up for a median of 114 days (IQR 113–194), and men for a median of 135 days (IQR 112–176).

Across women's visits, there were 300 HPV type-specific detections in 479 hand samples and 748 HPV types were detected in 483 vaginal samples. Across men's visits, 352 HPV types were detected in 489 hand samples and 903 HPV types were detected in 483 genital samples. The prevalence of at least one HPV type was 35% (170/479) in female hand samples, 36% (178/489) in male hand samples, 60% (283/473) in female genital samples, and 63% (306/483) in male genital samples (table 1). Across individual HPV types, the type-specific HPV prevalence was nearly always lower in hand than in genital samples (appendix).

The probability of detecting the same HPV type in both an individual's hand and genital samples was 16–18 times higher than expected if HPV types were independently distributed across hand and genital samples (figure 2A, B). The probability of detecting the same HPV type in both partners' hand or genital samples was 3·8–32·8 times higher than expected if HPV types were independently distributed across partnerships (figure 2C). This over-representation of partners concurrently positive for same-type HPV and under-representation of co-negative samples when a partner is HPV positive at any site would be expected if there is cross-site HPV transmission, either within individuals or between sex partners. Specifically, the lower than expected cases of same-type HPV hand positive samples and genital negative samples (observed:expected was 0·16 for men, 0·19 for women) compared with observed cases of same-type HPV hand-negative samples and genital-positive samples (observed:expected was 0·69 for both men and women) might reflect asymmetry in transmission or clearance between sites.

See Online for appendix

We present the probability of type-specific HPV positivity at a given site, stratified by sex and same-type HPV positivity at other sites (table 2). For instance, the probability of being hand HPV positive for a given type was 45% (141/312) for women and 54% (141/262) for men

	Exposure site positive			Exposure site negative			Univariate hazard ratio (95% CI)	Hazard ratio adjusted for all sites (95% CI)*
	Number at risk†	Events†	Incidence (per 100 years)	Number at risk†	Events†	Incidence (per 100 years)		
Women								
Incident hand positivity by exposure site								
Genital (own)	223	45	50·6	7218	33	1·0	51·0 (31·4–82·7)	17·9 (8·8–36·5)
Genital (partner)	284	39	32·5	6633	30	1·0	33·8 (20·2–56·5)	5·9 (2·8–12·4)
Hand (partner)	80	16	48·3	6909	54	1·7	26·7 (14·3–49·8)	1·4 (0·7–2·8)
Incident genital positivity by exposure site								
Hand (own)	34	5	29·9	7140	101	3·1	9·8 (3·8–25·4)	2·7 (0·8–8·5)
Genital (partner)	164	28	38·2	6435	62	2·1	19·2 (12·0–30·8)	19·3 (11·8–31·8)
Hand (partner)	41	3	15·5	6630	87	2·9	5·0 (1·5–16·4)	0·5 (0·1–1·8)
Men								
Incident hand positivity by exposure site								
Genital (own)	221	34	45·8	6496	42	1·6	27·4 (16·7–45·0)	7·2 (3·4–15·5)
Genital (partner)	170	28	50·2	6090	37	1·5	31·7 (18·5–54·2)	9·5 (4·3–21·1)
Hand (partner)	57	8	39·2	6238	57	2·3	14·3 (6·4–32·3)	1·0 (0·4–2·7)
Incident genital positivity by exposure site								
Hand (own)	25	3	29·8	6496	89	3·4	8·7 (2·6–29·5)	0·5 (0·1–3·1)
Genital (partner)	90	22	75·5	5921	58	2·4	33·3 (19·4–57·1)	28·4 (15·4–52·1)
Hand (partner)	37	8	59·5	6005	72	3·0	17·4 (7·9–38·5)	2·3 (0·9–6·2)

HPV=human papillomavirus. *Incident hand positivity: mutually adjusted for genital (own), genital (partner), and hand (partner) exposure site positivity; incident genital positivity: mutually adjusted for hand (own), genital (partner), and hand (partner) exposure site positivity. †The number at risk is 36 HPV types multiplied by the number of instances in which both the exposure and the outcome baseline site samples were valid and taken on the same day, and which have valid follow-up data for the outcome site. Total numbers at risk and number of events vary between rows because some individuals contributed to some analyses but not others if one of their samples is invalid.

Table 3: **Incidence rate and hazard ratios of type-specific incident hand and genital HPV DNA positivity stratified by HPV positivity at other sites at the previous visit, pooled over all HPV types**

if their partner's hand was positive for that type at the same visit. The probability of being genital HPV positive for a given type was 82% (243/297) for women and 85% (296/350) for men if their own hand sample was positive for that type at the same visit.

In the case of prevalent positivity, in univariate cross-sectional analyses (table 2), men and women were substantially more likely to be positive for a particular HPV type on their hands if their own genitals or their partner's hands or genitals were also positive for same HPV type. However, once we adjusted for positivity at all sites, HPV positivity in the hand was most strongly associated with same-type positivity in the individual's own genitals (table 2). Women were 49·5 times (95% CI 30·6–80·2) and men were 54·4 times (34·5–85·9) more likely to be positive for HPV on their hands if they were also positive for the same HPV type on their genitals than if they were negative in genital samples, after adjusting for HPV positivity of their partner's samples. Being positive for HPV on the hand was substantially less correlated with the partner's hand or genital status once we accounted for this intra-individual hand–genital correlation (table 2). The male partners who reported performing more hand-to-genital sex on their female partner had a higher probability of having a hand sample positive for the HPV types found on their partner's genitals, but the overall association was not significant (appendix). Individuals who had more frequent vaginal sex were more likely to have the same HPV type on their hand as on their partner's genitals compared with participants who had vaginal sex less often (odds ratio [OR] 2·1, 95% CI 1·1–3·9 for women and OR 2·7, 1·3–5·4 for men who have vaginal sex more than four times a week *vs* two times a week or less), but the relationship was not significant after we controlled for HPV positivity in their own genitals (appendix)·

In incident HPV analyses (table 3), once we adjusted for HPV positivity at all other sites at the previous visit, a woman was most likely to have an incident HPV detection on her hand if she was first positive on a genital sample for that HPV type at the previous visit. She was also significantly more likely to have incident HPV detected on her hand if her partner was positive for that HPV type in a genital sample, but not if he was positive for the same type in a hand sample at the previous visit. Adjusting for positivity at all other sites, a man was more likely to have incident HPV detected on his hand if he was first positive for that HPV type in a genital sample or if his partner was positive for the same type in a genital sample at the previous visit, but not if she was positive in a hand sample. Sensitivity analyses with interval-censored proportional hazard models provided very similar estimates (appendix).

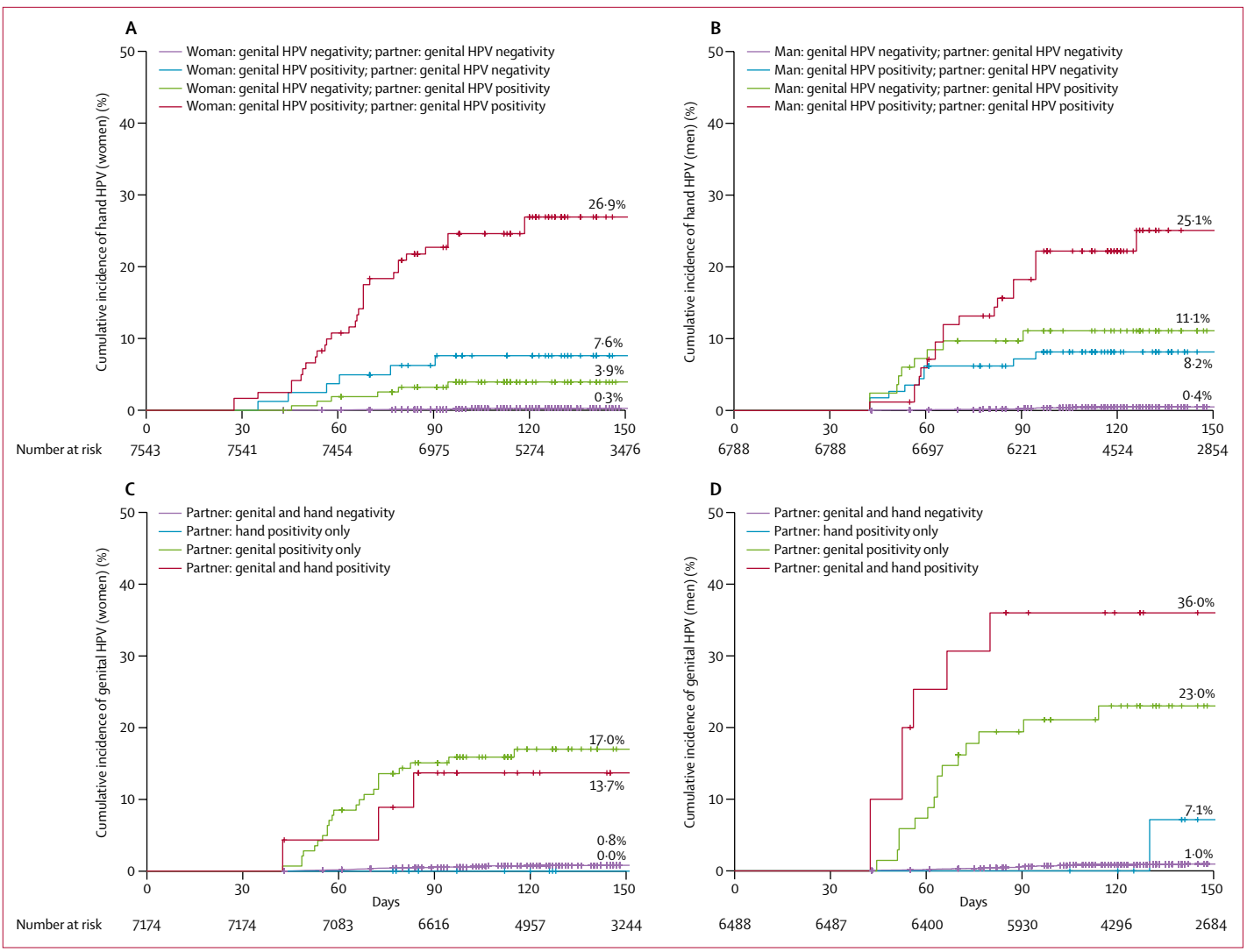

Figure 3: **Cumulative incidence of hand and genital type-specific HPV detections**
(A) Incident detections of HPV on hands in women. (B) Incident detections of HPV on hands in men. (C) Incident detections of HPV on the genitals of women and (D) men. Results are stratified by partner's hand and genital same-type HPV positivity at the previous visit, and by own same-type genital positivity at the previous visit (A and B). Results are pooled over all HPV types. HPV=human papillomavirus.

Kaplan-Meier curves of cumulative incident detection of HPV on the hands are presented in figure 3A, B.

For prevalent genital HPV, in univariate cross-sectional analyses (table 2), men and women were substantially more likely to be positive for an HPV type in a genital sample if their own hand or their partner's hand or genital samples were positive for the same HPV type. However, once adjusted for positivity at all sites, HPV positivity on the genitals was substantially less associated with positivity of the same type of HPV on the partner's hands. For example, although women were 105·6 times more likely to be positive for HPV in a genital sample if their partner was positive for the same type on his hand than if he was negative, this association declined to 4·1 (95% CI 2·7–6·3) controlling for being positive for the same type of HPV at other sites.

In the case of incident genital HPV, (table 3), once we adjusted for HPV positivity at all other sites, both women and men were most likely to have incident detection of HPV on the genitals if their partner was positive for the same type in a genital sample- taken at the previous visit. The incidence of detecting HPV in a genital sample was not significantly associated with participant's own or their partner's HPV positivity on the hand once we accounted for their partner's positivity for the same type of HPV in a genital sample taken at the previous visit. Sensitivity analyses with interval-censored proportional hazard models provided very similar estimates (appendix). Kaplan-Meier curves of cumulative incident detections of HPV in genital samples are presented in figure 3C, D. There were no incident detections of HPV in genital samples of women whose partner's hand was the only

HPV positive site at the previous visit (figure 3C). Only one incident detection of HPV89 in a genital sample was recorded from a man whose female partner's hand was the only HPV89-positive site at the previous visit (figure 3D); this man reported having ended the relationship and having new sexual partners during the interval, so he might have acquired HPV89 from another partner.

If an HPV type was detected in a hand sample, the probability of detecting the same type in a hand sample taken at the next visit was 26·4% (40/151, 95% CI 18·8–36·3) for women and 36·0% (58/161, 27·7–46·8) for men. If an HPV type was detected in a genital sample, the probability of detecting the same type in a genital sample taken at the next visit was 69·0% (234/339, 95% CI 60·6–78·6) for women and 75·2% (267/355, 66·6–84·9) for men.

Discussion

The importance of hand-to-genital transmission of HPV has been uncertain. Although some researchers have proposed that hand-to-genital transmission is plausible on the basis of a high concordance between hand and genital HPV types within individuals and between partners,[6,8] others have deemed this type of transmission unlikely, because of the transience of HPV detected on the hands[9] and doubts as to whether sufficient live virus is present on the hands or shed via exfoliation for successful transmission.[11] In this study, we found that the detection of alpha-type HPV on the hands is common in men and women, but that presence of HPV on the hands is most likely to concurrently occur with a same-type HPV genital infection. Alpha-HPV DNA detection on the hands alone without a same-type genital infection within the same individual or their sexual partner occurs substantially less often than expected by chance alone. Both HPV positivity on an individual's own genitals and their partner's genitals were important predictors of incident hand HPV detection. This finding suggests that the majority of alpha-HPV DNA detection on the hands in couples is due to self-inoculation from a person's own genitals or from the partner's genitals rather than hand-to-hand transmission. Conversely, being positive for an HPV type on the hands was not a significant predictor of incident detection of the same type in genital samples after we accounted for partner genital HPV positivity. This result suggests that the majority of incident genital infections are caused by genital-to-genital transmission, and that hand-to-genital transmission is unlikely to substantially contribute to the sexual transmission of alpha-HPV types.

We found similar cross-site concordance as previous studies,[8,9] which found that if HPV was detected on the hand, there was more than 60% probability that the person's or their partner's genitals were positive for the same type. Other groups have also estimated high genital-to-hand transmission.[7,8,10] A strength of this study relative to previous studies was that we had sufficient data to adjust our analyses for HPV positivity at different sites. This adjustment allowed us to study the direction of transmission while taking into account confounding due to other routes of transmission, which had been a major challenge for studying hand HPV transmission. Our results suggest that the high concordance of HPV detection on genitals and hands is due to genital-to-hand transmission rather than hand-to-genital transmission. A limitation of our data is that we had very few observations from individuals exposed to a partner who is positive for HPV only in a hand sample in incident genital detection analyses (17 for women and 17 for men), and that few couples in the HITCH study were not having vaginal sex. This factor limited our ability to completely rule out hand-to-genital HPV transmission. However, if hand-to-genital transmission does occur, our study suggests that it is unlikely to be an important mode of HPV transmission. The low prevalence of hand HPV positivity independent of genital positivity also further supports that the hand is unlikely to be an important reservoir of transmission. Although we did not find that the frequency of hand-to-genital sex was significantly associated with hand-genital HPV partner concordance, we had low statistical power for this analysis because few couples reported never having had hand-to-genital sex.

Determining whether the detection of HPV DNA represents an active infection at a site or merely the deposition of virions or free viral DNA is impossible. Participants had been asked to wash their hands with soap before sampling to reduce the likelihood of detecting contaminations in hand samples. We had concluded in a previous analysis that up to 14·1% of genital HPV detections in the HITCH study might be caused by partner deposition from recent sexual activity,[22] but the proportion of HPV DNA detected in the hand that represents deposition is unknown. The low persistence of HPV on the hand between visits in this and a previous study[9] suggests that many hand detections are likely to be depositions. Alpha-HPV types are thought to mostly infect the genitals or the oropharynx.[2] However, mouse models suggest that alpha-HPV infections might become established in cutaneous tissues after skin trauma.[23] Reports of cutaneous squamous cell carcinomas (Bowen's disease) on the hands linked with alpha-HPV types suggest that alpha-HPV can infect the hands in some cases.[5,24,25] The same HPV type is often found in both cervical and finger samples of patients with a history of both squamous cell carcinoma of the fingers and squamous cell carcinoma of the cervix.[25] Because the diagnosis of cervical cancer generally predates that of squamous cell carcinoma of the finger, this finding is also consistent with transmission mostly occurring from the genitals to hands. Regardless of whether HPV is present because of deposition or because of an active hand infection, we did not find that HPV detected on the hands substantially increased the risk of genital infection.

Compared with our study population, the general population is older and has a higher proportion of individuals who report no recent sexual partners or vaginal sex.[26] Therefore, most detections of HPV on the hands in the general population are likely to be due to self-inoculation rather than partner deposition, given that exposure to an infected partner is lower in the general population than in the study population. The associations we measured between HPV positivity in the genitals and hands are likely to be generalisable to most heterosexual populations. Our results might not be generalisable to non-heterosexual partnerships, because the relative importance of different modes of HPV transmission might be different.

The transmission modes of HPV are important for shaping the public health advice surrounding HPV. HPV testing is becoming widely implemented in many countries for cervical cancer screening. Increasing numbers of women are likely to learn for the first time that they are HPV positive and will have questions and concerns regarding their HPV diagnosis, including how they acquired it.[12,13] The information that HPV is largely transmitted by sexual genital contact might lead some to feel shame over having a sexually transmitted infection; however, the reassurance that HPV is highly common and that most people will become infected in their lifetime could reduce this stigma.[13,27] Given that transmission is most likely to occur from genital-to-genital contact, this could also be an opportunity to emphasise the preventive benefits of condoms to reduce HPV transmission to partners.[28] Clinicians might also reassure women that hand-to-genital transmission of HPV to self or to others is not as efficient a mechanism of transmission as genital intercourse, on the basis of our results.

Our results do not necessarily indicate that hand-to-genital HPV transmission does not occur, because rejecting rather than proving a null hypothesis of no transmission is easier. However, our study does bolster the assertion that if hand-to-genital transmission occurs, this type of transmission is unlikely to be important in genital HPV infections in sexual partnerships. Our study suggests that genital alpha-HPV detections are more likely to be caused by genital-to-genital transmission, and that most alpha-HPV DNA detections in the hand are likely to be caused by either genital-to-hand deposition or transmission (either from one's own genitals or from a partner's genitals). The high cumulative incidence of detection of HPV in the hand suggests that genital-to-hand HPV deposition is common. However, detection of HPV in the hand should not be cause for concern, because it is unlikely to substantially increase the risk of genital HPV transmission to oneself or to one's partners.

Contributors

ANB and ELF conceived and designed the HITCH study and obtained funding. ELF was the principal investigator for the study. ANB oversaw recruitment, data collection, provision of human papillomavirus test results to participants, and database design. P-PT oversaw clinical activities and recruitment. FC supervised the laboratory analyses and the quality of PCR assays. ME-Z, MW, and ANB managed the HITCH database. TM, KL, MW, and ELF designed the hand transmission analysis. TM and KL did the statistical analyses and wrote the first draft of the manuscript. All authors reviewed the manuscript for intellectual content and assisted in the interpretation of results.

Declaration of interests

TM and MW report postdoctoral grants from the Canadian Institutes of Health Research (CIHR) during the conduct of the study. ELF reports grants from CIHR, Merck, and the National Institutes of Health during the conduct of the study, and personal fees from Roche, Becton Dickinson, Merck, and GlaxoSmithKline, outside of the submitted work. FC reports grants from the Canadian Institutes of Health Research, the National Institutes of Health, and Merck during the conduct of the study, and grants, personal fees, and non-financial support from Roche and grants and personal fees from Merck and Becton Dickinson, outside the submitted work. KL, ANB, P-PT, and ME-Z declare no competing interests.

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References

1 Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S. Global burden of cancers attributable to infections in 2012: a synthetic analysis. *Lancet Glob Health* 2016; **4:** e609–16.

2 Egawa N, Egawa K, Griffin H, Doorbar J. Human papillomaviruses; epithelial tropisms, and the development of neoplasia. *Viruses* 2015; **7:** 3863–90.

3 Burchell AN, Winer RL, de Sanjosé S, Franco EL. Chapter 6: epidemiology and transmission dynamics of genital HPV infection. *Vaccine* 2006; **24:** S52–61.

4 Fairley CK, Gay NJ, Forbes A, Abramson M, Garland SM. Hand-genital transmission of genital warts? An analysis of prevalence data. *Epidemiol Infect* 1995; **115:** 169–76.

5 Mitsuishi T, Sata T, Matsukura T, Iwasaki T, Kawashima M. The presence of mucosal human papillomavirus in Bowen's disease of the hands. *Cancer* 1997; **79:** 1911–17.

6 Sonnex C, Strauss S, Gray JJ. Detection of human papillomavirus DNA on the fingers of patients with genital warts. *Sex Transm Infect* 1999; **75:** 317–19.

7 Hernandez BY, Wilkens LR, Zhu X, et al. Transmission of human papillomavirus in heterosexual couples. *Emerg Infect Dis* 2008; **14:** 888–94.

8 Widdice L, Ma Y, Jonte J, et al. Concordance and transmission of human papillomavirus within heterosexual couples observed over short intervals. *J Infect Dis* 2013; **207:** 1286–94.

9 Winer RL, Hughes JP, Feng Q, et al. Detection of genital HPV types in fingertip samples from newly sexually active female university students. *Cancer Epidemiol Biomarkers Prev* 2010; **19:** 1682–85.

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 Mindel A, Tideman R. HPV transmission—still feeling the way. *Lancet* 1999; **354:** 2097–98.

12 Patel H, Moss EL, Sherman SM. HPV primary cervical screening in England: women's awareness and attitudes. *Psychooncology* 2018; **27:** 1559–64.

13 McRae J, Martin C, O'Leary J, Sharp L. "If you can't treat HPV, why test for it?" Women's attitudes to the changing face of cervical cancer prevention: a focus group study. *BMC Womens Health* 2014; **14:** 64.

14 Burchell AN, Tellier PP, Hanley J, Coutlee F, Franco EL. Human papillomavirus infections among couples in new sexual relationships. *Epidemiology* 2010; **21:** 31–37.

15 Burchell AN, Tellier PP, Hanley J, Coutlee F, Franco EL. Influence of partner's infection status on prevalent human papillomavirus among persons with a new sex partner. *Sex Transm Dis* 2010; **37:** 34–40.

16 Burchell AN, Coutlée F, Tellier P-P, Hanley J, Franco EL. Genital Transmission of Human Papillomavirus in Recently Formed Heterosexual Couples. *J Infect Dis* 2011; **204:** 1723–29.

17 Burchell AN, Rodrigues A, Moravan V, et al. Determinants of prevalent human papillomavirus in recently formed heterosexual partnerships: a dyadic-level analysis. *J Infect Dis* 2014; **210:** 846–52.

18 Coutlee F, Rouleau D, Petignat P, et al. Enhanced detection and typing of human papillomavirus (HPV) DNA in anogenital samples with PGMY primers and the linear array HPV genotyping test. *J Clin Microbiol* 2006; **44:** 1998–2006.

19 Angelo C, Ripley B. boot: bootstrap R (S-Plus) functions. R package version 1.3–20; 2017.

20 Ripatti S, Palmgren J. Estimation of multivariate frailty models using penalized partial likelihood. *Biometrics* 2000; **56:** 1016–22.

21 Efron B. The efficiency of Cox's likelihood function for censored data. *J Am Stat Assoc* 1977; **72:** 557–65.

22 Malagon T, Burchell AN, El-Zein M, et al. Estimating HPV DNA deposition between sexual partners using HPV concordance, Y chromosome DNA detection, and self-reported sexual behaviors. *J Infect Dis* 2017; **216:** 1210–18.

23 Handisurya A, Day PM, Thompson CD, et al. Murine skin and vaginal mucosa are similarly susceptible to infection by pseudovirions of different papillomavirus classifications and species. *Virology* 2012; **433:** 385–94.

24 Clavel CE, Huu VP, Durlach AP, Birembaut PL, Bernard PM, Derancourt CG. Mucosal oncogenic human papillomaviruses and extragenital Bowen disease. *Cancer* 1999; **86:** 282–87.

25 Forslund O, Nordin P, Hansson BG. Mucosal human papillomavirus types in squamous cell carcinomas of the uterine cervix and subsequently on fingers. *Br J Dermatol* 2000; **142:** 1148–53.

26 Mercer CH, Tanton C, Prah P, et al. Changes in sexual attitudes and lifestyles in Britain through the life course and over time: findings from the National Surveys of Sexual Attitudes and Lifestyles (Natsal). *Lancet* 2013; **382:** 1781–94.

27 O'Connor M, Costello L, Murphy J, et al. 'I don't care whether it's HPV or ABC, I just want to know if I have cancer.' Factors influencing women's emotional responses to undergoing human papillomavirus testing in routine management in cervical screening: a qualitative study. *Bjog* 2014; **121:** 1421–29.

28 Winer RL, Hughes JP, Feng Q, et al. Condom use and the risk of genital human papillomavirus infection in young women. *New Engl J Med* 2006; **354:** 2645–54.