Epidemiology of sexually transmitted human papillomavirus infection in young females and their sequential male partners

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ABSTRACT

Background: The etiologic role of human papillomavirus (HPV) infections in cervical cancer is well established. Secondary cervical cancer prevention requires a detailed understanding of vaginal HPV infection natural history. Characterizing HPV transmission from previous sexual relationships to subsequent sex partners may have implications for primary HPV-related cancer prevention.

Objectives: Manuscript 1 examines detection and clearance rates for vaginal HPV infections among females in new heterosexual relationships. Manuscript 2 characterizes type-specific HPV positivity between sequential male partners of the same female.

Methods: Genital HPV genotyping and sexual behaviour data were collected on recently-paired Montréal couples in the HPV Infection and Transmission among Couples through Heterosexual activity (HITCH) prospective cohort study. Females provided vaginal samples at 0-, 4-, 8-, 12-, 18- and 24-months, while males provided scrotal and penile samples at 0- and 4-months. Data from 501 women (aged 18-24) were analyzed in Manuscript 1; time-to-event statistics for detection and clearance of HPV infections were calculated at the woman- and HPV-levels using Kaplan-Meier analysis and rates. Data from 42 female-linked sequential partnerships (42 male 1–42 female–42 male 2) were used in Manuscript 2; 1,512 detectable HPV infections were analyzed. Observed/expected ratios for infection concordance between males 1 and 2 were calculated. Using mixed-effects regression, odds ratios (ORs) for male 2 testing positive for the same HPV type as male 1 were estimated. 95% confidence intervals are provided in parentheses. Analyses were performed for any HPV type and by subgenera of the Alphapapillomavirus genus. Subgenus 1 includes low oncogenic risk HPV types, subgenus 2 high oncogenic risk types, and subgenus 3 commensal types.

Results: In Manuscript 1, by 24 months, one or more incident HPV infections were detected in 40.4% (33.4-48.4) of women. Incident subgenera 1, 2 and 3 infections cleared at comparable rates per 1000 infection-months: 43.4 (33.6-56.4), 47.1 (39.9-55.5) and 46.6 (37.7-57.7), respectively. In Manuscript 2, detection of the same HPV type in males 1 and 2 occurred 2.6 (1.9-3.5) times more often than chance. The OR for male 2 positivity was 4.2 (2.5-7.0). Adjusting for the number of times the linking female partner tested positive for the same HPV type attenuated the relationship between male 1 and 2 positivity.

Discussion: In Manuscript 1, HPV-level analyses did not clearly indicate that oncogenic subgenus 2 infections take longer to clear than low oncogenic-risk subgenera 1 and 3 infections. In Manuscript 2, type-specific HPV positivity in males 1 and 2 was not independent. OR estimates suggested mediation by the number of times the female tested positive; infections were likely transmitted to male 2 via the female.

Conclusions: Type-specific estimates of HPV infection natural history can provide biologically informed parameters for cervical screening. HPV positivity in male 1-female partnerships predicted positivity in male 2 when the linking female partner was persistently positive. Vaccinating males may therefore prevent HPV infection in unvaccinated ordinal sexual connections.

RÉSUMÉ

Contexte : Le rôle du virus du papillome humain (VPH) dans l'étiologie du cancer du col de l'utérus est bien établi. L'étude approfondie des infections vaginales par le VPH est nécessaire pour la prévention secondaire du cancer du col de l'utérus via le dépistage moléculaire du VPH. La caractérisation de la transmission du VPH des relations sexuelles antérieures aux partenaires sexuels suivants pourrait informer la prévention primaire des cancers liés au VPH.

Objectifs : Le premier manuscrit examine les taux de détection et de clairance des infections vaginales au VPH chez les femmes ayant de nouvelles relations hétérosexuelles. Le deuxième manuscrit caractérise les infections au VPH de type spécifique entre les partenaires mâles séquentiels d'une même femme.

Méthodes : Le génotype du VPH génital et les comportements sexuelles des couples montréalais récemment formés ont été collectés au cours de l'étude de cohorte prospective L'infection et la transmission du VPH chez les couples hétérosexuels (HPV Infection and Transmission among Couples through Heterosexual activity (HITCH)). Les participantes ont fourni des prélèvements vaginaux à 0, 4, 8, 12, 18 et 24 mois, tandis que les participants ont fourni des prélèvements de scrotum et de pénis à 0 et à 4 mois. Les données de 501 femmes (âgées de 18 à 24) ont été analysées au sein du manuscrit 1 ; nous avons utilisé les taux Kaplan-Meier pour analyser la détection et la clairance des infections par le VPH au niveau de la femme et au niveau du VPH. Les données de 42 partenariats séquentiels liés à des femmes (42 mâle 1-42 femelle-42 mâle 2) ont été analysés dans le manuscrit 2 ; 1 512 infections détectables au VPH. Les ratios observés/attendus de concordance des infections entre les mâles 1 et 2 ont été calculés. Nous avons estimé les rapports de cotes (OR), avec intervalles de confiance à 95%, pour le mâle 2 testant positif pour le même type de VPH que le mâle 1 à l'aide de la régression à effets mixtes. Les analyses ont été effectuées

pour chaque type de VPH et par sous-genre de Alphapapillomavirus. Le sous-genre 1 comprend les types de VPH faible risque oncogène, le sous-genre 2 comprend ceux à risque oncogène élevé et le sous-genre 3 comprend les types commensaux.

Résultats : Dans le manuscrit 1, après 24 mois de suivi, une ou plusieurs infections incidentes au VPH ont été détectées chez 40,4% (33,4-48,4) des femmes. Les taux de clairance des infections incidentes des sous-genres 1, 2 et 3 étaient comparables ; 43,4 (33,6-56,4), 47,1 (39,9-55,5) et 46,6 (37,7-57,7) par 1000 infections-mois, respectivement. Dans le manuscrit 2, la détection d'un même type de VPH chez les mâles 1 et 2 a eu lieu 2,6 (1,9-3,5) fois plus fréquemment que le hasard. Le OR pour la positivité du mâle 2 était de 4,2 (2,5-7,0). L'ajustement pour le nombre de fois que la femelle commune a testé positive pour ce même type de VPH a atténué la relation entre la positivé des mâles 1 et 2.

Discussion : Dans le manuscrit 1, les analyses au niveau du VPH n'indiquaient pas clairement que les infections du sous-genre 2 oncogénique étaient éliminées plus lentement que celles des sous-genres 1 et 3 à faible risque oncogène. Dans le manuscrit 2, la positivité spécifique au type de VPH chez les mâles 1 et 2 n'était pas indépendante. Les estimés des OR suggéraient que le nombre de fois que la femelle testait positive pour ce type agissait comme médiateur ; les infections chez le deuxième mâle étaient vraisemblablement transmises via la femelle.

Conclusions : Les estimés spécifiques au type de VPH de l'histoire naturelle de l'infection, peuvent fournir des paramètres pour le dépistage du cancer du col de l'utérus informés par la biologie. La positivité au VPH dans un partenariat mâle 1-femelle était un prédicteur de la positivité chez le mâle 2 lorsque la femelle commune était positive de façon persistante. La vaccination des mâles pourrait donc prévenir l'infection par le VPH chez les contacts sexuels ordinaux non-vaccinés.

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CONTRIBUTION OF AUTHORS

This thesis includes 2 original manuscripts. Both used data from the Human papillomavirus (HPV) Infection and Transmission among Couples through Heterosexual activity (HITCH) Cohort Study that was designed by Eduardo L. Franco and Ann N. Burchell. Eduardo L. Franco and Ann N. Burchell obtained funding. Eduardo L. Franco was the principal investigator for the study. Ann N. Burchell oversaw recruitment, data collection, provision of HPV test results to participants, and database design. Pierre-Paul Tellier oversaw clinical activities and recruitment. Francois Coutlée supervised laboratory analyses and the quality of polymerase chain reaction assays. Mariam El-Zein and Ann N. Burchell managed the HITCH database. Andrew W. Arthur performed statistical analyses and drafted the manuscripts under the supervision of Mariam El-Zein and Eduardo L. Franco. Ann N. Burchell provided statistical analysis consultation.

PREFACE

This thesis includes a literature review, methods, two original research manuscripts, and a discussion. Both manuscripts were prepared according to scientific journal submission guidelines; for continuity, prefixes have been added to all inserts. Tables, figures, and appendices are identified as belonging to Manuscript 1 (M1-), Manuscript 2 (M2-), or the Thesis as a whole (T-).

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LIST OF ACRONYMS & ABBREVIATIONS

ATP	Adenosine triphosphate
CI	Confidence interval
DNA	Deoxyribonucleic acid
HITCH	HPV Infection and Transmission among Couples through Heterosexual activity
HPV	Human papillomavirus
IQR	Interquartile range
KM	Kaplan-Meier
M1-	Manuscript 1 insert
M2-	Manuscript 2 insert
Male 1	Upstream male partner
Male 2	Downstream male partner
Mos.	Months
NA	Not applicable
NC	No concordance
NCE	No concordance expected
NR	Not reached
O/E	Observed/expected
OR	Odds ratio
p53	Tumor suppressor protein p53
pRB	Retinoblastoma protein
Reps.	Replications
STI	Sexually transmitted infection
T-	Thesis insert

CHAPTER 1. INTRODUCTION

1.1 RATIONALE

Human papillomavirus (HPV) is the most prevalent sexually transmitted infection (STI).[1] Persistent genital infections with oncogenic HPV genotypes (hereafter "HPV types") are a well-established necessary cause of cervical cancer.[2-4] Varying proportions of penile, anal, vulvar, vaginal, and head and neck cancers are also attributable to oncogenic HPV infection.[5] Sexually active young adults are at the highest risk of contracting HPV.[1] As a result, studies of heterosexual females and males in this age group have been essential in characterising infection transmission and natural history. Both HPV transmission and natural history are relevant to HPV-related cancer prevention planning, each for distinct reasons. Cervical cancer screening (i.e., secondary prevention) via molecular HPV testing relies on detailed type-specific HPV infection natural history data to optimize screening algorithms, particularly as a declining proportion of future cervical lesions result from infections with vaccine-preventable oncogenic HPV types.[6,7] Complementarily, a clear understanding of HPV transmission facilitates primary HPV-related cancer prevention by identifying best practices for minimizing incident oncogenic infections (e.g., vaccination targeting).

The HPV Infection and Transmission among Couples through Heterosexual activity (HITCH) prospective cohort study enrolled young adult females and their male partner(s).[8] The HITCH study has three features that are especially relevant to this thesis. Firstly, female and male sex partners provided genital samples longitudinally; samples were tested for 36 HPV types, facilitating the use of HPV infections as the units of analysis. Secondly, couples in the HITCH study were eligible only if they had been sexually active together for 6 months or less. New sex partners can expose each other to new HPV genotypes,[9-12] increasing infection incidence,

clearance, and transmission in the cohort. Finally, some females enrolled in the HITCH study recruited multiple male sex partners; therefore, HPV genotyping data are available for sequential male partners of the same female.

1.2 Objectives

Considering the HITCH study's unique positioning to provide evidence to inform primary and secondary HPV-related cancer prevention, we formulated two objectives: first, to study the natural history of type-specific genital HPV infections in young women; second, to characterize the transmission of HPV infections from one heterosexual partnership to a novel partner in the next. We addressed these objectives via two original research manuscripts.

1.3 Literature Review

1.3.1 Virology

Papillomaviruses are an ancient group of infectious agents commonly found in vertebrate epithelial tissues. HPV has a genetic propensity for infecting the epithelial tissue of *Homo sapiens* as a result of co-evolution in response to human epithelial tissue adaptations.[13] The HPV virion's approximately 8,000 base-pair circular DNA genome encodes 8 genes.[14] Each gene encodes one of 8 proteins – E6, E7, E1, E2, E4, E5, L2 and L1– all playing a role in the viral life cycle.[13]

During infection, the HPV virion accesses and binds to heparin sulfate proteoglycan receptors on keratinocyte stem cells in the basal layer of the epithelium via lesions (for instance, lesions induced by sexual activity).[13,15] After cell entry, gene expression is controlled by silencers, enhancers and promoters in the long control region at the start of the HPV genome.[14] This process allows the virus to modulate changes in infected epithelial cells as needed to perpetuate its life cycle. As infected keratinocytes mature and move toward the epithelial surface, E1 (ATP-dependent helicase) and E2 proteins upregulate HPV DNA production.[13] Signaling between the

long control region and infected cell facilitates E6 and E7 protein production. E6 proteins bind to tumor suppressor protein p53, and E7 proteins bind to retinoblastoma protein pRB, inactivating p53 and pRB.[14] Via the epidermal growth factor receptor, the E5 protein stimulates cell growth.[13] The combined result is cell proliferation in the spinous and granular layers of the upper epidermis.[15] As cells proliferate, new HPV genomes are packaged for viral release. The L1 gene produces the major capsid protein which gives the virion its bumpy, roughly spherical (icosahedral) shape. L2 minor capsid proteins are interspersed across the capsid.[14] The E4 protein promotes viral release about 3 weeks post-infection, in tandem with infected keratinocytes' migration through the epidermis and desquamation from the epidermal surface.[13-15]

1.3.2 Phylogenetic Classification

The L1 gene encodes hypervariable loops.[13] Unique HPV genotypes (HPV types) can be identified via polymerase chain reaction amplifying a segment of 450 base pairs on the L1 gene.[16] L1's hypervariability has informed the gene's use in distinguishing unique HPV types based on differences in nucleotide sequences ≥10%.[13]

The Alphapapillomavirus genus is a group of HPV types often found in the human anogenital region and oral mucosa. The genus can be divided into 3 subgenera, each with unique oncogenicity and tissue tropism properties. Subgenus 1 includes low oncogenic risk mucosal HPV types, subgenus 2 high oncogenic risk mucosal types, and subgenus 3 commensal, low oncogenic risk mucocutaneous types.[13,17] The HPV genome's long control region appears to regulate an HPV type's predilection for particular epithelial tissues. For example, mucosal HPV types may target stem cells in the cervix, while mucocutaneous types may target stem cells in the bulge region of the hair follicle.[13]

Oncogenic activity *and* viral persistence are both relevant to an HPV type's ability to induce malignant transformation.[17] High oncogenic risk types (i.e., subgenus 2 types) produce E6 and E7 proteins that bind more efficiently to tumor suppressor protein p53 and retinoblastoma protein pRB, compared to lower oncogenic risk types (e.g., subgenera 1 and 3 types). This may allow high oncogenic risk types to immortalize the cell and halt DNA repair, potentially inducing cancer development.[14] However, persistence of the viral infection is required to allow sufficient mutations to accumulate. E6 and E7 proteins produced by higher oncogenic risk HPV types may also downregulate interferon expression, which may help the infection circumvent immune surveillance and persist longer.[15] The most carcinogenic HPV types are characterised by both greater oncogenicity and ability to persist.[17]

1.3.3 Descriptive Epidemiology

HPV is the most common STI worldwide,[18] with young adults bearing the largest burden of prevalent infections.[1] An estimated 75% of women become infected with HPV at some point in their sexually active lifespan.[18] Genital infections are most prevalent in women shortly after sexual debut. Prevalence declines with age, which might be explained by the development of humoral immunity following sexual exposure to various HPV types. Infection prevalence increases again in post-menopausal women, the cause of which has not been definitively explained.[1] For male genital HPV positivity there is no age-related decline, but prevalence increases in both sexes with an increasing number of past sex partners.[18] Smoking, hormonal contraceptive use, earlier coitarche, concurrent STIs, intact foreskin, immune suppression, and an increasing number of births have been identified as factors that may raise the risk of prevalent or incident HPV infection.[1,18] It is not clear whether condom use reliably lowers the risk of infection,[1] possibly due to the virus's high transmissibility.[12]

1.3.4 Transmission

STI transmission is strongly influenced by two factors: sexual partnership timing and sexual networks. There is a limited window of time after STI infection where the infectious agent is (either sufficiently or maximally) transmissible to a sex partner. The time elapsed between infection acquisition and intercourse with a new sex partner/sex partners is therefore thought to be relevant to whether the infection is transmitted.[19] Each partner in a sexual relationship can have concurrent partners (i.e., multiple sex partners at once), or be serially monogamous (i.e., one sex partner at a time). Monogamy is the most common type of sexual partnership worldwide.[20] However, individuals with concurrent partners and individuals who are serially monogamous can both transmit STIs to their sex partner(s). One's odds of contracting an STI decline as the time since their sex partner's last sexual relationship grows longer.[19]

Additionally, an individual's position inside a sexual network is relevant to their risk of contracting and transmitting STIs. Sexual networks are branched maps that connect a population of individuals to their sex partners. These maps visualize one's ordinal sexual connections (i.e., 1° connections: sex partner(s), 2° connections: sex partner's partner(s), 3° connections: sex partner's partner's partner(s), etc.). Mathematical modelling has estimated that sexual connections as far away as 3° may be relevant to individual STI risk.[21] Persons with many direct and indirect sexual connections tend to be located in the core of the sexual network, and those with fewer connections tend to be on its periphery. It is thought that individuals in the core of the network drive epidemic STI increases while individuals in the periphery maintain endemic levels of infection.[22]

According to stochastic modelling based on HPV prevalence in young women, each act of intercourse carries a 40% HPV transmission probability, on average. Transmission is expected to be almost certain after 11 sex acts between partners.[12] This finding suggests HPV is considerably

more contagious via sexual contact compared to other viral STIs such as human immunodeficiency virus and herpes simplex virus-2.[12]

Couple-based studies have frequently used probability theory to examine HPV's sexual transmissibility. Using the prevalence of HPV in partners of each sex, these studies have calculated the number of couples expected to be concordant for HPV infection(s) by chance (further details in *Methods*). Observed concordance is consistently higher than expected by chance.[23-25] Higher-than-expected concordance between partners implies that the HPV positivity of current sex partners is not independent, which is a presumptive indication of HPV's sexual transmissibility.

Characterising incident HPV transmission requires prospective longitudinal HPV genotyping data for both individuals in an ongoing sexual partnership (i.e., data from longitudinal couple-based studies). As shown in T-Table 1, multiple couple-based studies have estimated genital HPV infection transmission to be a common occurrence in heterosexual couples. Of note, relatively high transmission rates were observed in the HITCH study, likely attributable to restriction to couples who recently initiated their sexual relationship.[26]

T-Table 1. Genital HPV transmission rates in longitudinal couple-based studies.[a]

Study	***n***	**Male→Female (95% CI)[b]**	**Female→Male (95% CI)[b]**
Hernandez et al., 2008[27]	25	45 (15-93)[27]	278 (190-383)[27]
Burchell et al., 2011[26]	179	35 (27-45)	40 (30-55)
Widdice et al., 2013[28]	25	92 (11-333)[c]	214 (78-465)[c]
Nyitray et al., 2014[29]	65	7 (4-14)	12 (7-20)
Liu et al., 2015[30]	296	7 (5-11)	6 (3-12)
Su et al., 2019[31]	97	12 (4-31)	11 (6-22)

Abbreviations: CI, confidence interval; HPV, human papillomavirus.

[a] Adapted from Balaji et al., 2020;[32] transmission rates for Hernandez et al., 2008 extracted from original article to include any male genital↔cervix/urine transmission.[27]

[b] Transmissions per 1000 person-months.

[c] Rate available for anogenital transmission only.

According to recent meta-analyzed estimates based on longitudinal couple-based studies, the preponderance of evidence favours a slightly higher rate of transmission in the female→male direction (30 transmissions per 1000 person-months) vs. the male→female direction (16 transmissions per 1000 person-months).[32]

1.3.5 Natural History

Several prospective cohort studies of young women have used longitudinal HPV genotyping data to characterise the incidence of HPV infections. One meta-analysis has estimated an incidence rate of 15.6 infections per 1000 woman-months.[33] The extent of heterogeneity between individual studies makes comparison of results somewhat difficult; HPV incidence is partially dependent on the number of HPV types genotyped and the composition of the study population (in particular, its age distribution). Nonetheless, as shown in T-Table 2, HPV incidence in young women is high, with 18-41% of women contracting at least one infection over a period of 1 year. Additionally, incidence is very similar comparing women who are sexually experienced to women who have had one lifetime sex partner,[34] or recently experienced coitarche.[9]

T-Table 2. Genital HPV incidence in longitudinal studies of young women.

Study	*n*	Age Range (years)	Incidence Rate (95% CI)[a]	1-Year Incidence (%)
Ho et al., 1998[35]	399	Mean: 20[b]	NA	20
Collins et al., 2002[34]	242	15-19	NA	Pre-Coitarche:[c] ~25[d]
Giuliano et al., 2002[11]	173	18-35	29 (21-41)	41
Richardson et al., 2003[36]	420	17-42	19 (16-22)	18
Winer et al., 2003[9]	444	18-20	NA	Pre-Coitarche:[c] ~30[d] Post-Coitarche:[c] ~22[d]
Ramanakumar et al., 2016[37]	553	15-25	21 (18-23)	29

Abbreviations: CI, confidence interval; HPV, human papillomavirus; NA, not available.

[a] Infections per 1000 woman-months.

[b] Range not provided.

[c] As of baseline.

[d] Extrapolated from Kaplan-Meier curve.

While HPV infections are exceptionally common, most are cleared by the immune system. Clearance appears to depend on cell-mediated immunity, since HPV-associated lesion regression involves a strong T cell, macrophage, cytokine and antibody response.[15] HPV infection clearance in women has a roughly exponential decay, with the clearance rate approaching 0 among still-persisting infections around 3 years.[38] HPV infections may persist as a result of various adaptions that allow the virus to evade the immune system indefinitely. For instance, HPV's lifecycle seems to be synchronized with that of keratinocytes. Keratinocytes' pre-programmed maturation and death are normal biological expectations in healthy individuals.[15] A lack of signals indicating abnormal activity makes it difficult for the immune system to detect the virus. Additionally, HPV virions may not activate antigen-presenting Langerhans cells, thereby hindering T cells' ability to initiate adaptive immunity.[15]

The typical persistence of an HPV infection is of great public health interest because infection persistence is necessary for the development of cervical cancer.[2-4] Cohort studies of young women have attempted to characterize infection persistence by measuring the time elapsed before HPV infection clearance. A meta-analysis of 15 infection natural history studies has approximated a median persistence of 9.8 months.[39] Similar to studies of HPV infection detection, comparison between infection persistence studies is challenging given different study designs, HPV genotyping strategies, and study population heterogeneity. Measurement of infection persistence is also sensitive to varying definitions of "infection clearance," and increasing time gaps between clinical sampling can overestimate the time at which infections clear. As demonstrated in T-Table 3, median persistence estimates from these studies vary greatly, from 8 to 17 months.

T-Table 3. Genital HPV persistence in longitudinal studies of young women.

Study	*n*	Age Range (years)	Median Persistence (months)
Ho et al., 1998[35]	175	Mean: 20[a]	8
Moscicki et al., 1998[40]	513	13-22	~8[b]
Woodman et al., 2001[41]	407	15-19	14
Giuliano et al., 2002[11]	NA	18-35	~9[b]
Richardson et al., 2003[36]	155	17-42	17
Ramanakumar et al., 2016[37]	320[c]	15-25	15

Abbreviations: HPV, human papillomavirus; NA, not available.

[a] Range not provided.

[b] Extrapolated from Kaplan-Meier curve.

[c] Extrapolated from incident infection count.

There is convincing evidence that some HPV infections that would traditionally be considered "cleared" remain present, dampened to a latent state by the immune system.[42] These infections generate HPV DNA at levels that are undetectable using current genotyping technologies, and may re-emerge in mid-adulthood following loss of immune control.[42]

1.3.6 Neoplastic Development

Although HPV infections are generally asymptomatic,[1] those that cause harm do so via neoplastic development. A small proportion of infections result in benign tumors and a smaller proportion result in malignant neoplasia, depending on the HPV type involved. HPVs 6 and 11 cause about 94% of condyloma acuminata (genital warts).[18] Genital warts often appear as smooth tumors on the cervix, and keratotic tumors elsewhere.[18] With an estimated prevalence of 1% in the sexually active United States population,[43] genital warts are a common consequence of HPV infection.

Most of our knowledge on type-specific HPV oncogenicity comes from HPV types' involvement in invasive cervical cancer. The vast majority of HPV-related malignant neoplasia is caused by HPVs 16, 18, 31, 33, 35, 45, 52 and 58. There is less certain, but convincing evidence

that HPVs 39, 51, 56 and 59 also cause a small proportion of malignant neoplasia.[44] For this reason, all aforementioned types are considered definite carcinogens by the International Agency for Research on Cancer.[2,44] Persistent infection with oncogenic HPV types is a necessary cause of cervical cancer, with 99.7% of cervical carcinomas containing HPV DNA or other viral components.[3] HPVs 16 and 18, in particular, are present in roughly 70% of invasive cervical cancer cells.[44] While epidemiologic data are limited in their ability to verify the oncogenicity of subgenus 2 HPV types not aforementioned, their shared phylogenetic lineage suggests they are capable of carcinogenicity, regardless of whether they ultimately induce malignant transformation.[17,44] Infections caused by many Alphapapillomavirus HPV types are capable of persisting, but only persistent infections with types belonging to subgenus 2 present an elevated risk of progressing cervical cells to a severe dysplastic or cancerous state.[17]

Minor subclinical cytological abnormalities are probable in HPV-infected individuals (observed in ¼ to ½ of HPV DNA positive women).[38] However, the relative risk of cervical neoplasia increases as the infection persists longer.[4] Precancer can develop within 2-20 years of infection.[14,38] Generally, infections that progress cervical cells to neoplasia are thought to be abortive (i.e., infections no longer efficiently replicating the HPV virion), characterised by overexpression of oncoproteins E6 and E7.[13] HPV-related cancers may occur more often in epithelial cell types that don't support productive HPV infections, possibly explaining higher risks of cancer at anatomical sites that high oncogenic risk types preferentially infect.[13]

While the risk of cervical precancer/cancer posed by persistent HPV infection often drowns out the impact of other risk factors, among the best-characterized are smoking, increasing numbers of births, and extended use of hormonal contraceptives.[38]

1.3.7 HPV-Related Cancer Burden

According to 2020 GLOBOCAN estimates, with about 604,000 cases and 342,000 deaths, cervical cancer is the second most common and second most lethal cancer in females, worldwide.[45] As shown in T-Table 4, other HPV-related cancers are not 100% attributable to HPV infection. However, HPV is responsible for most anal, vaginal, and penile cancers, worldwide.

T-Table 4. Estimated global burden of HPV-related cancers in 2020, by site.

Site	2020 Global Incidence (*n*)[45]	HPV-Attributable Burden (%)[5]
Cervical Cancer	604,127	100
Anal Cancer	50,865	88
Vaginal Cancer	17,908	78
Penile Cancer	36,068	51
Vulvar Cancer	45,240	15-48[a]
Oropharyngeal Cancer	98,412	13-60[b]
Laryngeal Cancer	184,615	5
Cancer of the Oral Cavity	377,713	4

[a] Dependent on age.

[b] Dependent on world region.

1.3.8 Primary HPV-Related Cancer Prevention

Prophylactic HPV vaccines create adaptive immunity by exposing immune cells to empty viral shells composed of L1 capsid proteins, which induces the production of HPV type-specific antigen-neutralizing IgG antibodies.[15] Three Health Canada authorized vaccines provide coverage for different combinations of HPV types: CERVARIX® (GSK plc, United Kingdom) prevents infection with HPVs 16 and 18; GARDASIL® (Merck Group, Germany) prevents infection with HPVs 6, 11, 16, and 18; and GARDASIL9® (Merck Group, Germany) prevents infection with HPVs 6, 11, 16, 18, 31, 33, 45, 52, and 58. Vaccine efficacy in preventing infection with covered HPV types is high – for instance, 98% for the first-authorized vaccine, GARDASIL®.[46] Three years after GARDASIL®'s introduction in the United States, the prevalence of HPVs 6, 11, 16, and 18 in the first cohort of vaccine-eligible females halved (compared to three years before introduction).[47] About 90% of HPV-positive invasive cervical cancer cells are positive for a

GARDASIL9®-preventable HPV type, as well as 96%, 63%, and 25% of female anal, vaginal, and vulvar cancers, respectively.[6]

Males also gain protection from HPV-related cancers via vaccination. However, the burden of male HPV-related cancers is roughly 9% of the burden of female HPV-related cancers.[5] As a result, gender-neutral HPV vaccination is controversial. A key source of controversy relates to herd immunity in STI vaccination contexts. Herd immunity occurs when a vaccinated persons' immunity to HPV stops them from contracting and therefore transmitting the virus. Infection prevalence in the population decreases, protecting unvaccinated individuals as a side-effect. Because STI transmission requires sexual contact between two people, and the majority of the population prefers sexual contact with the opposite sex, one sex benefits from herd effects when only the opposite sex is vaccinated.[48,49] Due to herd immunity gained by heterosexual males via female-only HPV vaccination, vaccinating both males and females is generally not considered cost-effective.[50] However, elimination of the most oncogenic HPV type, HPV16, is only likely when 4 in 5 people of *both* sexes are vaccinated.[50] Additionally, since males tend to have more sexual partners than females,[20] and herd effects are stronger when STI vaccination is targeted toward persons with higher risk sexual behaviour,[21,48] it is possible that vaccinating males may exert greater herd effects than vaccinating females. There are also a number of ethical implications to female-only vs. gender-neutral vaccination, ranging from the lack of secondary prevention options for male HPV-related cancers, to the absence of herd immunity benefits for unvaccinated men who have sex with men and transfeminine persons.[51]

1.3.9 Secondary Cervical Cancer Prevention

While Pap cytology has been the dominant secondary cervical cancer prevention strategy for decades, molecular HPV testing's superior sensitivity in detecting cervical precancer[52] will

continue to inform its substitution as the optimal technique for opportunistic and organized cervical screening programs over the coming years. Molecular HPV testing uses HPV positivity as a predictor of precancerous lesion presence. As HPV vaccination prevents an increasing share of oncogenic HPV infections, the incidence of precancerous lesions will decline. Since molecular HPV testing's positive predictive value is dependent on the prevalence of precancerous lesions in the population, the test's ability to identify women who truly have cervical lesions will decrease with time.[7]

Molecular HPV testing's performance may need to be re-evaluated in response to fewer vaccine-preventable infections – a process which relies on mathematical modelling. Given the HPV type-dependent nature of cervical carcinogenesis, such models will require parameters informed by granular type-specific estimates of HPV infection natural history.

CHAPTER 2. METHODS

Below is a discussion of methodological constructs that permeate chapters 3 and 4 of this thesis. To avoid unnecessary repetition, full methodologies for manuscripts 1 and 2 are available in sections 3.2.3 and 4.2.3. The following descriptions add granularity and may be used as a reference throughout for additional detail.

2.1 HPV-Level Analysis & Intraparticipant Correlation

We used the Linear Array genotyping assay (F. Hoffmann-La Roche AG, Switzerland) to test for 36 HPV types in genital samples provided by participants in the HITCH study. The linear array assay is well-established and widely used in epidemiologic studies of HPV infection and transmission.[16] For each visit attended, there were up to 36 virological outcomes for each participant. The most efficient and infection biology-informed analysis strategy for the resulting data uses the HPV infection as the unit of analysis (i.e., HPV-level analysis). While HPV type-specific, this strategy requires more elaborate statistical methods to account for potential intraparticipant correlation arising from HPV genotypes' shared transmission route.[53,54]

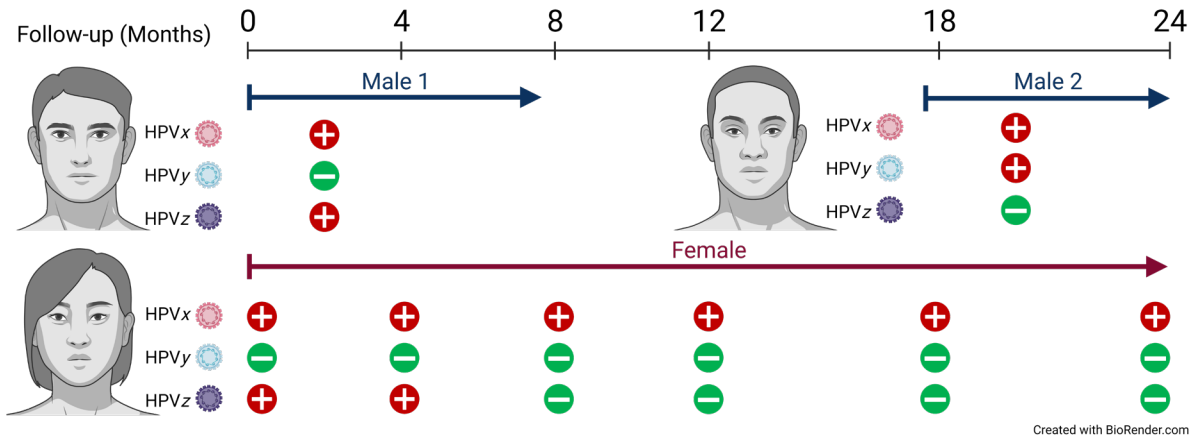
In Manuscript 1, we account for potential intraparticipant correlation using participant-cluster adjusted Clopper-Pearson confidence intervals,[55] participant-clustered jackknife procedures, and participant-cluster resampling bootstrap procedures.[56] In Manuscript 2, we account for potential intra-linked partnership correlation using linked partnership-cluster resampling bootstrap procedures and mixed-effects logistic regression models with an exchangeable correlation structure.[53,57,58]

2.2 Male Genital Samples

In Manuscript 2, we used penile and scrotal samples to assess genital HPV positivity in male HITCH study participants. The adequacy of male genital samples has presented challenges

in past HPV infection and transmission studies. HITCH study nurses exfoliated and swabbed epithelial cells from the scrotum, glans penis, external meatus, coronal sulcus, penile shaft, and foreskin (when present). While this strategy produces a high percentage of male samples with adequate cellularity (97%),[59] we validated the cellularity of individual specimens by coamplifying β-globin DNA during HPV genotyping.[8]

Given loss-to-follow-up among males, we assessed agreement for type-specific HPV positivity between male genital samples at multiple visits. Ultimately, we combined HPV positivity for each male into a single measure per HPV type. An exemplar schematic of HPV positivity for participants in one female-linked partnership is provided in T-Figure 1, for reference.



T-Figure 1. HPV positivity at the HPV-level across follow-up for one female-linked partnership.

2.3 Probability Analysis

We used probability theory to characterise transmission between sexual partnerships in Manuscript 2. Defining concordance between males 1 and 2 as detection of the same HPV type in both males, we calculated their expected concordance, assuming their positivity statuses were independent. Given this assumption, the number of infections for which males 1 and 2 are expected

to be concordant is equal to the product of HPVx's prevalence (P) in each male, divided by the total number of detectable HPVx infections (T):

$$Expected\ Concordance = \frac{P_{HPVx\ Male1} \times P_{HPVx\ Male2}}{T_{HPVx}}$$

By comparing the resultant value to the observed male 1: male 2 concordance, we approximated whether indirect transmission between sequential male partners of the same female was likely:

$$Observed/Expected\ Ratio = \frac{Observed\ Male\ 1: Male\ 2\ Concordance_{HPVx}}{\frac{P_{HPVx\ Male1} \times P_{HPVx\ Male2}}{T_{HPVx}}}$$

2.4 Mediation Analysis

In Manuscript 2, to determine whether infection persistence in the linking female partner mediated the relationship between male 1 and male 2 HPV positivity, we used a traditional approach to mediation analysis. First, we regressed male 2 positivity (the outcome) onto male 1 positivity (the exposure) to determine the odds of male 2 testing positive for the same HPV type as male 1. Then, we adjusted the model for the number of instances in which the linking female partner tested positive for the same HPV type. When the female positivity covariate nullified the association between male 1 and male 2 positivity, we considered female positivity to be a potential mediator, given it's ability to explain the association between male 1 and male 2 HPV positivity.[60]

CHAPTER 3. HPV NATURAL HISTORY IN YOUNG FEMALES

3.1 PREFACE

Several studies have characterized the detection and/or clearance of genital HPV infections in young women.[9,11,33-37,39-41,61-63] We saw an opportunity to characterize HPV natural history in greater depth, using an HPV-level analysis approach.

All females enrolled in the HITCH study initiated a sexual relationship with their male partner within 6 months prior to enrolment.[8] Past studies have identified novel male partners as a risk factor for incident HPV infections in young women.[9-11] As a result, we expected HPV infections to be relatively common in this cohort. The multiplicity of infections presented an opportunity to characterize the natural history of individual HPV types split by their presence or absence at baseline (i.e., incident infection detection, clearance of infection present at baseline, and clearance of incident infection). We believe these results to be the most detailed description of HPV natural history in young women to-date, and expect that this level of detail will be necessary in cervical screening models and algorithms as HPV vaccination causes cervical lesion prevalence to decline, and as the share of lesions caused by vaccine-preventable types dwindles.[7]

Past studies have generally performed natural history analyses at the woman-level (i.e., the woman was the unit of observation). While easy to interpret, woman-level survival analysis estimates are only capable of accounting for one event per participant (i.e., detection of many HPV types is considered one detection, clearance of all types is considered one clearance). However, multiple HPV types can be transmitted synchronously during sexual contact,[38] which suggests these simplifications might impact study results. HPV-level analyses treat the infection as the unit of observation and can therefore account for multiple detection or clearance events per woman.

The results of our analysis are presented in Manuscript 1. *Detection and clearance of type-specific and phylogenetically related genital human papillomavirus infections in young women in new heterosexual relationships* was made available as a preprint on medRxiv.org[64] and submitted for peer review to *The Journal of Infectious Diseases* (Oxford University Press) on February 24th, 2023. Portions of this manuscript were presented at a McGill University Department of Oncology seminar on March 11th, 2022, the 22nd Annual McGill Biomedical Graduate Conference on March 22nd, 2022, the McGill University Faculty of Medicine and Health Sciences Celebration of Research and Training in Oncology on June 21st, 2022, and the 2023 Canadian Society for Epidemiology and Biostatistics Conference on June 28th, 2023.

3.2 DETECTION AND CLEARANCE OF TYPE-SPECIFIC AND PHYLOGENETICALLY RELATED GENITAL HUMAN PAPILLOMAVIRUS INFECTIONS IN YOUNG WOMEN IN NEW HETEROSEXUAL RELATIONSHIPS

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3.2.1 Abstract

Background. Understanding the natural history of human papillomavirus (HPV) infections is essential to effective cervical cancer prevention planning. We examined these outcomes in-depth among young women.

Methods. The HPV Infection and Transmission among Couples through Heterosexual Activity (HITCH) study is a prospective cohort of 502 college-age women who recently initiated a heterosexual relationship. We tested vaginal samples collected at six clinical visits over 24 months for 36 HPV types. Using rates and Kaplan-Meier analysis, we estimated time-to-event statistics with 95% confidence intervals (CIs) for detection of incident infections and liberal clearance of incident and present-at-baseline infections (separately). We conducted analyses at the woman- and HPV-levels, with HPV types grouped by phylogenetic relatedness.

Results. By 24 months, we detected incident infections in 40.4%, CI:33.4-48.4 of women. Incident subgenus 1 (43.4, CI:33.6-56.4), 2 (47.1, CI:39.9-55.5) and 3 (46.6, CI:37.7-57.7) infections cleared at similar rates per 1000 infection-months. We observed similar homogeny in HPV-level clearance rates among present-at-baseline infections.

Conclusions. Our woman-level analyses of infection detection and clearance agreed with similar studies. However, our HPV-level analyses did not clearly indicate that high oncogenic risk subgenus 2 infections take longer to clear than their low oncogenic risk and commensal subgenera 1 and 3 counterparts.

Keywords: Papillomaviridae, human papillomavirus, sexually transmitted infection, genital infection, prospective cohort study, incidence, clearance, persistence, natural history, cervical cancer

3.2.2 Introduction

In 2020, cervical cancer accounted for 3.1% of the global cancer burden (604,127 cases) [1]. Persistent genital infection with oncogenic types of human papillomavirus (HPV) is a necessary cause of the majority of cervical precancerous lesions and cancers [2-6]. While most infections in young women are transient, a minority persist [7], and a sizeable proportion of "incident" infections in older women are reactivations of previously undetectable infections acquired earlier in life [8].

Cervical cancer is a highly preventable disease. The nonavalent HPV vaccine prevents infection with HPV types found in 89.5% of invasive cervical cancers [9], and molecular HPV testing is an efficacious screening strategy [10]. Studies of HPV infection natural history in young women [11-23] have provided parameters for models and algorithms that inform primary and secondary cervical cancer prevention strategies.

In these studies, the woman was the unit of observation (i.e., analyses were conducted at the woman-level). Woman-level analyses incorporate the detection or clearance of multiple HPV infections into composite outcomes, which can obscure detections and clearances of multiple individual infections in the same woman. HPV-level analyses (where the HPV infection is the unit of observation), have a stronger biological rationale for characterising infection natural history because they treat the detection and clearance of each unique infection as a separate HPV type-specific event.

We described vaginal HPV infection prevalence, incidence (i.e., time to detection), and persistence (i.e., time to clearance) with respect to individual HPV types, as well as types grouped by subgeneric classifications using woman-level and HPV-level paradigms. We based our analyses on a cohort of women who had recently initiated a new sexual relationship with a male partner in

the HPV Infection and Transmission among Couples through Heterosexual activity (HITCH) study.

3.2.3 Methods

i. Study Design and Procedures

We used data from female participants of the HITCH prospective cohort study. Study details have been published elsewhere [24]. Briefly, we recruited female university and college students (aged 18-24) who began a sexual relationship with a male partner ≤ 6 months prior. Enrolment occurred between 2005 and 2011 in Montréal, Canada, at university-run health clinics. At baseline, 4-, 8-, 12-, 18- and 24-months post-enrollment, women provided a vaginal sample and completed sociodemographic/sexual behavioural questionnaires. Women were asked to refrain from sexual activity for 24 hours before each visit. Based on nurse instructions, participants self-collected vaginal samples using a polyester swab. The diagnostic accuracy of self-sampling has been demonstrated [25-27]. We used the Linear Array genotyping assay (Roche Molecular Systems, CA) to detect (individually) 36 HPV types [28], validating samples via β-globin DNA coamplification. After the 2006 licensing of the HPV vaccine, women were asked how many doses they had received. The HITCH study was approved by the Institutional Review Boards of McGill and Concordia Universities as well as the Centre Hospitalier de l'Université de Montreal; participants provided written informed consent.

ii. Taxonomic Groups

We described the natural history of individual HPV types separately. We did the same for three groups of phylogenetically related HPV types, as defined by subgenera of the Alphapapillomavirus genus. This taxonomic scheme clusters HPV types according to tissue tropism and oncogenic risk, based on empirical evidence and differential mucosotropic type

distributions. Subgenus 1 includes low oncogenic risk HPVs 6, 11, 40, 42, 44, and 54; subgenus 2 includes high oncogenic risk HPVs 16, 18, 26, 31, 33, 34, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73 and 82; and subgenus 3 includes commensal HPVs 61, 62, 71, 72, 81, 83, 84 and 89 [29-31]. Analyses designated "Any HPV" or "All HPV," incorporate all 36 types.

iii. Analytical Frameworks

We performed analyses at the woman-level (see M1-Addenda 1 and 2) and the HPV-level (see M1-Addendum 3). We analysed the outcome "single detection" of incident infections (M1-Figure 1A). Woman-level detection occurred the first time a woman tested positive for the HPV type(s) of interest, whereas HPV-level detection occurred each first time a woman tested positive for a distinct type of interest. To restrict to incident detections, we excluded women positive for the type(s) of interest at baseline from woman-level analyses, and types of interest women were positive for at baseline from HPV-level analyses.

We then analyzed the outcome "liberal clearance." Woman-level clearance occurred the first time a woman tested negative for all type(s) of interest after testing positive for one (or more) types of interest, whereas HPV-level clearance occurred each first time a woman tested negative for a distinct type of interest following a positive test for the same type. We analysed liberal clearance in the context of infections present at baseline (M1-Figure S1) and incident infections (M1-Figure 1B) separately. To restrict to infections present at baseline, we included women who were positive for the type(s) of interest at baseline from woman-level analyses, and types of interest women were positive for at baseline from HPV-level analyses. To restrict to incident infections, we included women who were initially negative, then later positive for the type(s) of interest in woman-level analyses, and types of interest for which women were initially negative, then later positive in HPV-level analyses.

We repeated all analyses substituting more stringent outcome definitions: double detection and conservative clearance. These outcomes were akin to single detection and liberal clearance (respectively) on the woman- and HPV-levels, however, the defining positive/negative results occurred at two consecutive visits. We measured times to these more-stringent events based on the first of the two positive/negative visits.

iv. Statistical Analyses

The ability to detect multiple HPV types in the same genital sample can generate intraparticipant correlation; for all HPV-level analyses, we selected statistical approaches that account for data clustering (detailed below). We calculated, by visit, HPV prevalence with 95% exact confidence intervals (CIs). For HPV-level analyses, we accounted for intra-woman clustering using a degrees of freedom-adjusted effective sample size [32].

We estimated Kaplan-Meier (KM) product-limit rates at 6, 12, and 24 months to describe cumulative detection and percent of infections uncleared. Using the log-log approach, we assigned 95% CIs to woman-level estimates. For HPV-level estimates, we assigned pointwise percentile-based woman-clustered bootstrap 95% CIs [33, 34].

We estimated the rate of detection/clearance per 1000 woman-months for woman-level analyses, and per 1000 infection-months for HPV-level analyses. 95% CIs around rates were estimated via quadratic approximation of Poisson log-likelihood for woman-level analyses. We extracted 95% CIs from a leave-one-woman-cluster-out jackknife procedure for HPV-level analyses.

We calculated all mean and median times to detection/clearance including censored observations (i.e., actuarial measures of central tendency), then excluding censored observations

(i.e., outcome-conditional measures of central tendency). We estimated mean times to detection/clearance (restricted to longest follow-up) with parametric 95% CIs for woman-level analyses, and percentile-based woman-clustered bootstrap 95% CIs for HPV-level analyses. Based on the log-log survival function CIs, we assigned 95% CIs to the woman-level median, and based on the woman-clustered bootstrap survival function CIs, we assigned 95% CIs to the HPV-level median.

We performed sensitivity analyses to approximate the extent to which right censoring caused actuarial mean times to detection/clearance to be underestimated. We calculated a separate mean time to each event based on the area under a KM survival function with a fitted exponential decay to $S(t) = 0$ (hereafter exponentially-extended mean). For woman-level analyses, we assigned percentile-based bootstrap 95% CIs; for HPV-level analyses, bootstraps were resampled by woman-clusters. Statistical analyses were conducted using Stata SE 17.0 (StataCorp LLC., TX).

3.2.4 Results

Of 502 women enrolled, 453 provided two or more valid vaginal samples; 48 had only one valid sample and were included in prevalence estimates but not survival analyses. For six women missing a valid vaginal sample at baseline, we treated samples provided at visit 2 as baseline samples. Loss-to-follow-up by visit 6 was 43.7% (M1-Figure S2). Among the 453 women included in survival analyses, median follow-up was 26.4 (quartiles 1-3: 19.5-31.7) months. Most women identified with the following ethnicities: English Canadian (34.0%), French Canadian (27.3%), Italian (4.6%), Latin American (4.9%), and Multiple or Mixed Ethnicities (5.1%). At baseline, the mean age was 20.7 years (standard deviation: 1.8). Women reported an average weekly vaginal intercourse frequency of 4.6 and, on average, 6.4 previous heterosexual relationships involving

vaginal sex. Among 93 women who reported having received the HPV vaccine, the mean number of doses was 2.6.

As shown in M1-Table 1, the three most prevalent HPV types at baseline were HPV16 (16.8%, CI:13.6-20.3), HPV89 (10.6%, CI:8.0-13.6), and HPV51 (10.2%, CI:7.7-13.2). Across follow-up, HPV16 (10.7-16.8%) and HPV89 (9.5-10.6%) remained among the three most-prevalent types. At baseline, the prevalence of any HPV infection was 57.1%, CI:52.6-61.5 at the woman-level (n_w=501), and 4.3%, CI:3.9-4.8 at the HPV-level (n_{HPV}=18,036).

M1-Table 2 summarizes single detection of incident HPV infections. Among women negative for all HPV types at baseline, cumulative detection of any incident infection was 40.4%, CI:33.4–48.4 by 24 months. The detection rate for any type was 20.0, CI:16.1-24.9 per 1000 woman-months. Rates per 1000 woman-months were higher for subgenus 2 types (17.0, CI:13.7-20.9) compared to subgenera 1 (11.4, CI:9.3-13.9) and 3 (12.4, CI:10.1-15.1). KM graphs for single detection are displayed in M1-Figure 2 (woman-level) and M1-Figure S3 (HPV-level). M1-Table S1 alongside M1-Figures S4 and S5 reproduce the aforementioned results for double detection analyses.

M1-Tables 3 and 4 summarize liberal clearance analyses of present-at-baseline and incident infections, respectively. At the woman-level, the median times to clearance of all present-at-baseline and incident infections were 27.0, CI:25.0-32.7 and 22.3, CI:16.2-NR months, respectively (NR: CI bound Not Reached). At the HPV-level, the median time required to clear HPV infections of any type was similar between infections present at baseline (11.7, CI:10.3-12.6 months) and incident infections (12.6, CI:10.3-14.8 months). The rate of clearing infections of any HPV type per 1000 infection-months was different between infections present at baseline (61.3, CI:56.2-66.9) and incident infections (46.2, CI:41.1-52.0) at the HPV-level. This difference in

rates was not observable at the woman-level (23.6 vs. 25.5 per 1000 woman-months). M1-Figure 3 depicts, at the woman-level, survival functions for liberal clearance analyses; M1-Figure S6 presents the same at the HPV-level. In HPV-level liberal clearance analyses, a larger proportion of incident infections (35.4%) were right censored compared to infections present at baseline (23.7%).

At the woman-level, among infections present at baseline, we observed a lower clearance rate per 1000 woman-months (27.4, CI:22.6-33.2), and a longer median time to clearance (23.7, CI:20.0-26.1 months) of all subgenus 2 infections compared to subgenera 1 (rate 56.6, CI:44.0-72.7; median 11.5, CI:8.5-13.5 months) and 3 (rate 45.8, CI:36.6-57.4; median 14.2, CI:11.3-17.8 months). Among incident infections, the clearance rate per 1000 woman-months (47.2, CI:34.1-65.5), and median time to clearance (13.5, CI:9.4-18.5 months) of all subgenus 2 infections were similar to those of subgenera 1 (rate 45.6, CI:32.7-63.5; median 14.3, CI:9.9-17.6 months) and 3 (rate 51.0, CI:37.4-69.6; median 14.4, CI:10.8-19.7 months).

At the HPV-level, however, there was homogeny within infections present at baseline and within incident infections when estimating the time to clearance of subgenus 2 infections compared to subgenera 1 and 3 infections. Amongst infections present at baseline, rates of clearing any infection of subgenera 1, 2, and 3 were 65.8, CI:53.9-80.3; 60.5, CI:55.4-66.2; and 61.0, CI:50.6-73.3 per 1000 infection-months, respectively. The corresponding median infection durations were 10.6, CI:8.1-12.5; 12.1, CI:10.8-13.2; and 10.4, CI:8.5-13.1 months, respectively. Amongst incident infections, rates of clearing any infection of subgenera 1, 2, and 3 were 43.4, CI:33.6-56.4; 47.1, CI:39.9-55.5; and 46.6, CI:37.7-57.7 per 1000 infection-months, respectively. The corresponding median infection durations were 13.1, CI:9.9-17.6; 12.7, CI:9.4-15.1; and 12.2, CI:9.7-15.1 months, respectively. The percent of right-censored infections in HPV-level grouped

analyses was similar for subgenera 1, 2, and 3 within analyses of infections present-at-baseline (24.0%, 23.7%, and 23.2%, respectively) and within analyses of incident infections (37.5%, 35.0%, and 34.6%, respectively). M1-Tables S2 and S3, alongside M1-Figures S7 and S8 reproduce the aforementioned results for conservative clearance analyses.

Exponentially-extended means (calculated using a survival function extended to 0) are presented in M1-Tables S4 (time to detection) and S5 (time to clearance). The average differences between exponentially-extended and actuarial mean times to single detection were 1538.7 months for individual HPV types, 28.4 months for grouped types at the woman-level, and 363.5 months for grouped types at the HPV-level, respectively. These large average differences suggest the mean time to detection was unreliable. For liberal clearance analyses, the corresponding average differences were 1.4, 3.1, and 0.2 months for infections present at baseline and 1.7, 6.2, and 7.3 months for incident infections. These small average differences suggest the mean time to clearance was reliable.

3.2.5 Discussion

This study described the natural history of vaginal HPV infections in young women who recently initiated a new sexual relationship. We found a high prevalence, high detection rate, low clearance rate, and long average duration of HPV16 infections compared to other HPV types, consistent with previous studies [11, 12, 14-16, 18-21]. We observed a higher woman-level rate of detection for any HPV type compared to pooled rates in women under 30 years of age (20.0 vs. 15.6 detections per 1000 woman-months, respectively) [12]. By 24 months, we estimated a similar cumulative detection of any HPV to those reached by 24 to 36 months in studies of similarly-aged or slightly younger women [15, 20, 21] and by 12 months in a study of slightly older young women [14]. 24-month cumulative detection and rate of detection in this cohort are comparable to a

205 previous study of college-age women in Montréal [19]. The most likely explanation for the
206 observed high rates of HPV detection in this cohort is that all women had recently begun a new
207 sexual relationship at enrollment. A new sexual partner represents a potential for exposure to new
208 HPV infection(s). In support of this explanation, a similar cumulative detection rate has been
209 observed by 24 months in women with only one partner post sexual debut [13]. Testing for many
210 HPV types may also have played a role in the observed high detection rate.

211 The woman-level rate of incident subgenus 2 (i.e., oncogenic) infection detection was
212 higher than the corresponding rates for subgenera 1 and 3. This finding is consistent with several
213 studies observing elevated detection rates among high-risk types [12]. While we did not use the
214 traditional high-risk vs. low-risk HPV type grouping scheme, comparing subgenus 2 types to
215 subgenera 1 and 3 types (i.e., high oncogenic risk types vs. low oncogenic risk & commensal types)
216 is a viable analogue based on biological rationale.

217 Our woman-level estimates of median time to clearance of all infections present at baseline
218 (27.0 months) and clearance of all incident infections (22.3 months) were larger than a meta-
219 analyzed estimate based on studies that included prevalent and/or incident infections (9.8 months)
220 [11]. In particular, it took women in our study longer, on average, to clear all incident infections
221 compared to an earlier cohort of college-age women in Montréal [19]. Follow-up intervals in the
222 present cohort were spaced similarly to those of the earlier study per protocol (4-6 months vs. 6
223 months, respectively). However, three-quarters or more women attended follow-up visits late in
224 the present cohort, so interval censoring may have artificially prolonged the time to infection
225 clearance.

226 In HPV-level analyses, the median duration of infection with any HPV type was similar
227 between incident and present-at-baseline infections, though the clearance rate was higher for those

present at baseline. However, our analysis of incident infections was more prone to right-censoring than our analysis of infections present at baseline, so we cannot rule out the possibility that women were under observation for an inadequate period to clear incident infections, artificially lowering the corresponding clearance rate estimate.

Among women with infections at baseline, we observed a lower woman-level clearance rate and longer median time to clearance of all subgenus 2 infections compared to subgenera 1 and 3. A meta-analysed estimate [11] and several longitudinal studies specific to young women [5, 14, 17-19] corroborate lower woman-level clearance rates for high-risk vs. low-risk HPV types.

A lower rate of, and longer median time to clearance might suggest that subgenus 2 (i.e., oncogenic) infections are more persistent than infections belonging to other subgenera. However, woman-level analyses are limited in their ability to accurately estimate infection persistence. Woman-level clearance events are only counted when a woman tests negative for all HPV types within the grouping of interest. Assuming the null hypothesis, *Subgenus 2 infections are no more persistent than infections of other subgenera*, clearing (up to) twenty-two subgenus 2 infections is of lower probability than clearing (up to) six subgenus 1, or eight subgenus 3 infections. Past studies have generally genotyped more high- than low-risk HPV types, which creates a similar conundrum. In contrast to woman-level analyses, HPV-level analyses treat the clearance of each unique infection as a separate event. This is a more biologically-informed paradigm for understanding the natural history of individual HPV infections.

In our HPV-level analyses, we did not observe systematic differences in the persistence of high oncogenic risk subgenus 2 infections compared to low oncogenic risk subgenera 1 and 3 infections, as indicated by clearance rate and median time to clearance. This was the case for both incident and present-at-baseline infections. It is unlikely that these results are an artefact of disproportional

censoring, since subgenus 2 infections were no more right censoring-prone than infections belonging to other subgenera. Altogether, our woman-level findings corroborate previous studies with respect to the persistence of oncogenic infections, while our HPV-level findings do not.

The limitations of this study relate to infection latency, HPV DNA deposition, interval censoring, and estimation of the mean time to detection. First, HPV latency muddles assumptions defined in our analytical frameworks. We attempted to maximize infections acquired during current sexual relationships in analyses of incident infections by including only women/HPV types that were negative at baseline. However, some "incident" infections may be reactivations of latent infections [8]. Latent reactivations have the same HPV positivity signature as incident detections. While the two phenomena are impossible to distinguish, we previously estimated that in the HITCH study, up to 39% of incident infection detections are attributable to latent reactivation [35]. The transition of an infection into a latent state also has the same positivity signature as liberal clearance. To counter the effects of latency, we performed more stringent analyses that reject single-visit reactivation (i.e., double detection) and single-visit latency (i.e., conservative clearance) as events. We attempted to maximize infections acquired during previous relationships in analyses of infections present at baseline by including only women/HPV types that were positive at baseline. However, these infections may have been transmitted by the current male partner in the (up to) 6 months of sexual activity allowed before baseline. Secondly, although women were asked to refrain from sex for 24 hours before providing specimens, a substantial proportion of samples may be false positives as a result of HPV DNA deposition from a male partner [36]. Thirdly, due to interval censoring, discrete times assigned to all HPV results surpass true viral infection and clearance. Our analyses overestimate the times at which incident infections are acquired and present-at-baseline infections are cleared. The time elapsing between detection and

clearance of incident infections could be over- or under-estimated, depending on the extent of pre-detection left censoring and post-clearance right censoring. Interval censoring may have also bypassed transient infections (decreasing detection rates) and overlooked clearances that occurred before re-infection (increasing average time to clearance). Fourthly, according to our sensitivity analyses, actuarial mean times to detection were unreliable estimates as a result of heavy right censoring [37]. We were limited in our ability to estimate central tendency for time to detection, since many detection analyses did not reach the 50^{th} percentile required to estimate a median. Fortunately, the actuarial mean was a reliable indicator of average time to clearance.

Our woman-level analyses largely corroborated similar past studies. However, our HPV-level analyses did not clearly indicate that high oncogenic risk subgenus 2 HPV infections are more persistent than their low oncogenic risk and commensal subgenera 1 and 3 counterparts. Our HPV-level estimates of infection natural history provide biologically-informed parameters for cervical cancer prevention planning, specifically with respect to the persistence of oncogenic subgenus 2 infections.

3.2.6 Notes

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301 ***Author contributions.*** E.L.F. and A.N.B. designed HITCH and obtained funding. E.L.F. was the
302 principal investigator for the study. A.N.B. oversaw recruitment, data collection, provision of HPV
303 test results to participants, and database design. P.P.T. oversaw clinical activities and recruitment.
304 F.C. supervised laboratory analyses and the quality of polymerase chain reaction assays. M.E.Z.
305 and A.N.B. managed the HITCH database. A.W.A. performed statistical analyses and drafted the
306 manuscript under the supervision of M.E.Z. and E.L.F.. A.N.B. provided statistical analysis
307 consultation. All authors read, provided feedback, and approved the final manuscript.

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309 of Oncology, McGill University and a presenter's award from the Experimental Medicine
310 Graduate Students' Society, McGill University. M.E.Z. and E.L.F. hold a patent related to the
311 discovery "DNA methylation markers for early detection of cervical cancer," registered at the
312 Office of Innovation and Partnerships, McGill University, Montréal, Québec, Canada (October
313 2018). A provisional utility patent application before the United States Patent and Trademark
314 Office was also filed (November 2018) and a patent cooperation treaty application
315 (PCT/IB2020/050885), filed in February 2020, has been published (no. WO 2020/115728; June
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Dickinson outside of the submitted work. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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Data availability. HITCH participant consent forms specified that data would be published in aggregate form and that individual-level data would only be available to study investigators. To access individual-level data, please contact Eduardo Franco at eduardo.franco@mcgill.ca. The protocol for the HITCH cohort study has been published [24]. Analytical codes and data dictionary are available on the McGill University Dataverse [38].

Disclaimer. The funders played no role in study design, data collection/analysis, preparation of the manuscript, or the decision to submit it for publication.

Ethics approval. All subjects provided written informed consent for study participation and use of their biological specimens in future studies. HITCH complies with all national/international regulations regarding research with human data and materials, including the Declaration of Helsinki. The study was conducted per the principles and articles stipulated by the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. Ethical approval was obtained from the institutional review boards at McGill University, Concordia University, and the Centre Hospitalier de l'Université de Montréal. Ethics renewal approval is requested annually from McGill University (study number A09-M77-04A).

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3.2.8 Tables & Figures

M1-Table 1. Prevalence at each visit [$n_{positive}$, % (95% CI)] of individual HPV types, grouped types at the woman-level, and grouped types at the HPV level per visit, by subgenus. Sample size at each visit is reported for woman- (n_w) and HPV- (n_{HPV}) level analyses.

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	n_w=501, n_{HPV}=18,036	n_w=451, n_{HPV}=16,236	n_w=412, n_{HPV}=14,832	n_w=374, n_{HPV}=13,464	n_w=326, n_{HPV}=11,736	n_w=282, n_{HPV}=10,152
Subgenus 1						
HPV6	19, 3.8 (2.3, 5.9)	17, 3.8 (2.2, 6.0)	19, 4.6 (2.8, 7.1)	22, 5.9 (3.7, 8.8)	21, 6.4 (4.0, 9.7)	18, 6.4 (3.8, 9.9)
HPV11	3, 0.6 (0.1, 1.7)	0, 0.0 (0.0, 0.8)[a]	0, 0.0 (0.0, 0.9)[a]	1, 0.3 (0.0, 1.5)	2, 0.6 (0.1, 2.2)	1, 0.4 (0.0, 2.0)
HPV40	12, 2.4 (1.2, 4.2)	6, 1.3 (0.5, 2.9)	9, 2.2 (1.0, 4.1)	12, 3.2 (1.7, 5.5)	8, 2.5 (1.1, 4.8)	7, 2.5 (1.0, 5.1)
HPV42	38, 7.6 (5.4, 10.3)	43, 9.5 (7.0, 12.6)	32, 7.8 (5.4, 10.8)	21, 5.6 (3.5, 8.5)	24, 7.4 (4.8, 10.8)	23, 8.2 (5.2, 12.0)
HPV44	10, 2.0 (1.0, 3.6)	6, 1.3 (0.5, 2.9)	5, 1.2 (0.4, 2.8)	5, 1.3 (0.4, 3.1)	7, 2.2 (0.9, 4.4)	5, 1.8 (0.6, 4.1)
HPV54	30, 6.0 (4.1, 8.4)	23, 5.1 (3.3, 7.6)	16, 3.9 (2.2, 6.2)	18, 4.8 (2.9, 7.5)	16, 4.9 (2.8, 7.9)	14, 5.0 (2.7, 8.2)
Any Woman-Level	98, 19.6 (16.2, 23.3)	80, 17.7 (14.3, 21.6)	72, 17.5 (13.9, 21.5)	65, 17.4 (13.7, 21.6)	65, 19.9 (15.7, 24.7)	56, 19.9 (15.4, 25.0)
Any HPV-Level[b]	112, 0.6 (0.5, 0.8)	95, 0.6 (0.5, 0.7)	81, 0.6 (0.4, 0.7)	79, 0.6 (0.5, 0.8)	78, 0.7 (0.5, 0.8)	68, 0.7 (0.5, 0.9)
Subgenus 2						
HPV16	84, 16.8 (13.6, 20.3)	66, 14.6 (11.5, 18.2)	59, 14.3 (11.1, 18.1)	40, 10.7 (7.8, 14.3)	37, 11.4 (8.1, 15.3)	33, 11.7 (8.2, 16.0)
HPV18	18, 3.6 (2.1, 5.6)	13, 2.9 (1.5, 4.9)	8, 1.9 (0.8, 3.8)	9, 2.4 (1.1, 4.5)	11, 3.4 (1.7, 6.0)	10, 3.6 (1.7, 6.4)
HPV26	0, 0.0 (0.0, 0.7)[a]	0, 0.0 (0.0, 0.8)[a]	0, 0.0 (0.0, 0.9)[a]	1, 0.3 (0.0, 1.5)	0, 0.0 (0.0, 1.1)[a]	0, 0.0 (0.0, 1.3)[a]
HPV31	24, 4.8 (3.1, 7.0)	25, 5.5 (3.6, 8.1)	20, 4.9 (3.0, 7.4)	15, 4.0 (2.3, 6.5)	17, 5.2 (3.1, 8.2)	12, 4.3 (2.2, 7.3)
HPV33	8, 1.6 (0.7, 3.1)	2, 0.4 (0.1, 1.6)	4, 1.0 (0.3, 2.5)	2, 0.5 (0.1, 1.9)	0, 0.0 (0.0, 1.1)[a]	1, 0.4 (0.0, 2.0)
HPV34	3, 0.6 (0.1, 1.7)	1, 0.2 (0.0, 1.2)	0, 0.0 (0.0, 0.9)[a]	0, 0.0 (0.0, 1.0)[a]	2, 0.6 (0.1, 2.2)	0, 0.0 (0.0, 1.3)[a]
HPV35	4, 0.8 (0.2, 2.0)	4, 0.9 (0.2, 2.3)	5, 1.2 (0.4, 2.8)	5, 1.3 (0.4, 3.1)	3, 0.9 (0.2, 2.7)	1, 0.4 (0.0, 2.0)
HPV39	34, 6.8 (4.8, 9.4)	32, 7.1 (4.9, 9.9)	18, 4.4 (2.6, 6.8)	22, 5.9 (3.7, 8.8)	15, 4.6 (2.6, 7.5)	15, 5.3 (3.0, 8.6)
HPV45	8, 1.6 (0.7, 3.1)	8, 1.8 (0.8, 3.5)	3, 0.7 (0.2, 2.1)	5, 1.3 (0.4, 3.1)	6, 1.8 (0.7, 4.0)	8, 2.8 (1.2, 5.5)
HPV51	51, 10.2 (7.7, 13.2)	41, 9.1 (6.6, 12.1)	32, 7.8 (5.4, 10.8)	20, 5.4 (3.3, 8.1)	19, 5.8 (3.6, 9.0)	19, 6.7 (4.1, 10.3)
HPV52	35, 7.0 (4.9, 9.6)	28, 6.2 (4.2, 8.9)	29, 7.0 (4.8, 10.0)	22, 5.9 (3.7, 8.8)	15, 4.6 (2.6, 7.5)	15, 5.3 (3.0, 8.6)
HPV53	36, 7.2 (5.1, 9.8)	35, 7.8 (5.5, 10.6)	35, 8.5 (6.0, 11.6)	29, 7.8 (5.3, 11.0)	23, 7.1 (4.5, 10.4)	16, 5.7 (3.3, 9.1)
HPV56	25, 5.0 (3.3, 7.3)	21, 4.7 (2.9, 7.0)	15, 3.6 (2.1, 5.9)	13, 3.5 (1.9, 5.9)	11, 3.4 (1.7, 6.0)	7, 2.5 (1.0, 5.1)
HPV58	23, 4.6 (2.9, 6.8)	20, 4.4 (2.7, 6.8)	16, 3.9 (2.2, 6.2)	16, 4.3 (2.5, 6.9)	13, 4.0 (2.1, 6.7)	9, 3.2 (1.5, 6.0)
HPV59	30, 6.0 (4.1, 8.4)	21, 4.7 (2.9, 7.0)	16, 3.9 (2.2, 6.2)	11, 2.9 (1.5, 5.2)	15, 4.6 (2.6, 7.5)	11, 3.9 (2.0, 6.9)
HPV66	31, 6.2 (4.2, 8.7)	30, 6.7 (4.5, 9.4)	20, 4.9 (3.0, 7.4)	20, 5.4 (3.3, 8.1)	16, 4.9 (2.8, 7.9)	12, 4.3 (2.2, 7.3)
HPV67	28, 5.6 (3.8, 8.0)	22, 4.9 (3.1, 7.3)	20, 4.9 (3.0, 7.4)	16, 4.3 (2.5, 6.9)	14, 4.3 (2.4, 7.1)	5, 1.8 (0.6, 4.1)
HPV68	14, 2.8 (1.5, 4.6)	11, 2.4 (1.2, 4.3)	13, 3.2 (1.7, 5.3)	10, 2.7 (1.3, 4.9)	8, 2.5 (1.1, 4.8)	7, 2.5 (1.0, 5.1)
HPV69	0, 0.0 (0.0, 0.7)[a]	0, 0.0 (0.0, 0.8)[a]	0, 0.0 (0.0, 0.9)[a]	0, 0.0 (0.0, 1.0)[a]	0, 0.0 (0.0, 1.1)[a]	0, 0.0 (0.0, 1.3)[a]
HPV70	4, 0.8 (0.2, 2.0)	3, 0.7 (0.1, 1.9)	5, 1.2 (0.4, 2.8)	5, 1.3 (0.4, 3.1)	5, 1.5 (0.5, 3.5)	3, 1.1 (0.2, 3.1)
HPV73	18, 3.6 (2.1, 5.6)	17, 3.8 (2.2, 6.0)	19, 4.6 (2.8, 7.1)	13, 3.5 (1.9, 5.9)	11, 3.4 (1.7, 6.0)	11, 3.9 (2.0, 6.9)
HPV82	14, 2.8 (1.5, 4.6)	7, 1.6 (0.6, 3.2)	5, 1.2 (0.4, 2.8)	6, 1.6 (0.6, 3.5)	3, 0.9 (0.2, 2.7)	2, 0.7 (0.1, 2.5)
Any Woman-Level	240, 47.9 (43.5, 52.4)	207, 45.9 (41.2, 50.6)	192, 46.6 (41.7, 51.6)	151, 40.4 (35.4, 45.5)	139, 42.6 (37.2, 48.2)	107, 37.9 (32.3, 43.9)
Any HPV-Level[b]	492, 2.7 (2.4, 3.1)	407, 2.5 (2.2, 2.9)	342, 2.3 (2.0, 2.7)	280, 2.1 (1.8, 2.5)	244, 2.1 (1.8, 2.5)	197, 1.9 (1.6, 2.3)
Subgenus 3						
HPV61	12, 2.4 (1.2, 4.2)	13, 2.9 (1.5, 4.9)	15, 3.6 (2.1, 5.9)	13, 3.5 (1.9, 5.9)	12, 3.7 (1.9, 6.3)	14, 5.0 (2.7, 8.2)
HPV62	40, 8.0 (5.8, 10.7)	43, 9.5 (7.0, 12.6)	32, 7.8 (5.4, 10.8)	28, 7.5 (5.0, 10.6)	24, 7.4 (4.8, 10.8)	22, 7.8 (5.0, 11.6)
HPV71	2, 0.4 (0.1, 1.4)	1, 0.2 (0.0, 1.2)	0, 0.0 (0.0, 0.9)[a]	0, 0.0 (0.0, 1.0)[a]	0, 0.0 (0.0, 1.1)[a]	0, 0.0 (0.0, 1.3)[a]
HPV72	2, 0.4 (0.1, 1.4)	2, 0.4 (0.1, 1.6)	1, 0.2 (0.0, 1.3)	1, 0.3 (0.0, 1.5)	1, 0.3 (0.0, 1.7)	1, 0.4 (0.0, 2.0)

HPV81	8, 1.6 (0.7, 3.1)	7, 1.6 (0.6, 3.2)	4, 1.0 (0.3, 2.5)	0, 0.0 (0.0, 1.0)[a]	0, 0.0 (0.0, 1.1)[a]	3, 1.1 (0.2, 3.1)
HPV83	9, 1.8 (0.8, 3.4)	10, 2.2 (1.1, 4.0)	6, 1.5 (0.5, 3.1)	8, 2.1 (0.9, 4.2)	4, 1.2 (0.3, 3.1)	3, 1.1 (0.2, 3.1)
HPV84	48, 9.6 (7.2, 12.5)	38, 8.4 (6.0, 11.4)	32, 7.8 (5.4, 10.8)	19, 5.1 (3.1, 7.8)	14, 4.3 (2.4, 7.1)	24, 8.5 (5.5, 12.4)
HPV89	53, 10.6 (8.0, 13.6)	45, 10.0 (7.4, 13.1)	39, 9.5 (6.8, 12.7)	36, 9.6 (6.8, 13.1)	26, 8.0 (5.3, 11.5)	23, 8.2 (5.2, 12.0)
Any Woman-Level	133, 26.6 (22.7, 30.6)	120, 26.6 (22.6, 30.9)	99, 24.0 (20.0, 28.5)	77, 20.6 (16.6, 25.1)	65, 19.9 (15.7, 24.7)	72, 25.5 (20.6, 31.0)
Any HPV-Level[b]	174, 1.0 (0.8, 1.1)	159, 1.0 (0.8, 1.2)	129, 0.9 (0.7, 1.1)	105, 0.8 (0.6, 1.0)	81, 0.7 (0.5, 0.9)	90, 0.9 (0.7, 1.1)
All 36 Types						
Any Woman-Level	286, 57.1 (52.6, 61.5)	249, 55.2 (50.5, 59.9)	227, 55.1 (50.2, 60.0)	192, 51.3 (46.1, 56.5)	168, 51.5 (46.0, 57.1)	141, 50.0 (44.0, 56.0)
Any HPV-Level[b]	778, 4.3 (3.9, 4.8)	661, 4.1 (3.6, 4.6)	552, 3.7 (3.3, 4.2)	464, 3.5 (2.9, 4.0)	403, 3.4 (2.9, 4.0)	355, 3.5 (3.0, 4.1)

Abbreviations: CI, confidence interval; HPV, human papillomavirus.

[a] Type not detected. One-sided 97.5% CI assigned.

[b] Degrees of freedom-adjusted effective sample size used to account for intra-woman clustering.

M1-Table 2. Single detection of incident infection for individual HPV types, grouped types at the woman-level, and grouped types at the HPV-level, by subgenus.

	n[a]	Cumulative Detection of Infection, % (95% CI)			Detection Rate[b] (95% CI)	Time (months) to Detection (95% CI)			
		6 Months	12 Months	24 Months		Actuarial Mean[c]	Actuarial Median[c]	Conditional Mean[d]	Conditional Median[d]
Subgenus 1									
HPV6	435	0.7 (0.2, 2.1)	3.4 (2.1, 5.7)	7.5 (5.3, 10.8)	3.8 (2.8, 5.2)	44.8 (43.1, 46.5)	NR	17.3 (14.5, 20.1)	17.0 (11.5, 19.7)
HPV11	451	0.0[e]	0.0[e]	0.9 (0.3, 2.8)	0.4 (0.1, 0.9)	48.9 (48.3, 49.5)	NR	23.2 (16.0, 30.4)	19.6 (14.9, NR)
HPV40	442	0.0[e]	1.0 (0.4, 2.6)	4.2 (2.5, 6.9)	1.9 (1.3, 2.9)	46.5 (44.6, 48.4)	NR	19.7 (15.9, 23.4)	16.8 (14.0, 23.9)
HPV42	419	2.7 (1.5, 4.8)	6.0 (4.1, 8.9)	9.7 (7.1, 13.2)	5.1 (3.9, 6.7)	43.5 (41.8, 45.1)	NR	16.0 (13.2, 18.7)	12.9 (9.6, 22.0)
HPV44	445	0.2 (0.0, 1.6)	0.7 (0.2, 2.2)	1.3 (0.5, 3.0)	0.9 (0.5, 1.7)	48.2 (47.4, 49.0)	NR	20.0 (13.6, 26.4)	16.8 (4.2, 29.2)
HPV54	426	0.7 (0.2, 2.2)	1.8 (0.8, 3.6)	5.4 (3.5, 8.3)	2.7 (1.9, 3.9)	46.3 (45.1, 47.4)	NR	19.0 (15.7, 22.3)	18.0 (15.3, 23.7)
Any Woman-Level	367	3.6 (2.1, 6.1)	10.6 (7.8, 14.3)	21.5 (17.3, 26.5)	11.4 (9.3, 13.9)	38.2 (36.2, 40.1)	NR	16.3 (14.5, 18.1)	15.4 (12.3, 18.0)
Any HPV-Level[f]	2,618	0.7 (0.4, 1.1)	2.1 (1.5, 2.9)	4.8 (3.8, 6.1)	2.4 (2.0, 2.9)	46.4 (44.2, 47.0)	NR	17.8 (16.0, 19.5)	17.0 (14.9, 19.7)
Subgenus 2									
HPV16	374	1.6 (0.7, 3.6)	2.5 (1.3, 4.8)	6.9 (4.6, 10.3)	3.3 (2.4, 4.8)	45.5 (44.1, 46.9)	NR	18.0 (14.7, 21.3)	17.5 (12.2, 22.3)
HPV18	437	0.2 (0.0, 1.6)	1.0 (0.4, 2.6)	1.9 (0.9, 4.1)	1.1 (0.6, 2.0)	48.0 (47.2, 48.8)	NR	20.0 (14.4, 25.6)	22.7 (8.4, 31.1)
HPV26	453	0.0[e]	0.0[e]	0.3 (0.0, 1.9)	0.1 (0.0, 0.6)	49.4 (49.2, 49.5)	NR	--	NR
HPV31	430	1.0 (0.4, 2.5)	2.5 (1.3, 4.6)	4.2 (2.6, 6.8)	2.4 (1.6, 3.5)	45.3 (43.7, 46.9)	NR	17.4 (13.4, 21.4)	13.7 (10.6, 25.0)
HPV33	448	0.0[e]	0.5 (0.1, 2.0)	1.0 (0.4, 2.7)	0.5 (0.2, 1.2)	48.6 (47.7, 49.4)	NR	18.8 (10.9, 26.7)	13.1 (9.6, NR)
HPV34	450	0.0[e]	0.0[e]	0.6 (0.1, 2.3)	0.2 (0.0, 0.7)	49.3 (49.0, 49.5)	NR	17.6 (12.4, 22.8)	13.8 (13.8, NR)
HPV35	450	0.2 (0.0, 1.6)	0.5 (0.1, 1.9)	1.0 (0.4, 2.7)	0.4 (0.2, 1.1)	48.9 (48.5, 49.4)	NR	15.2 (6.9, 23.4)	12.0 (4.6, NR)
HPV39	421	1.2 (0.5, 2.9)	2.0 (1.0, 3.9)	5.9 (3.9, 8.9)	2.6 (1.8, 3.8)	46.3 (45.1, 47.6)	NR	16.4 (13.0, 19.9)	15.3 (11.4, 20.2)
HPV45	445	0.7 (0.2, 2.1)	0.7 (0.2, 2.1)	2.1 (1.1, 4.2)	1.3 (0.8, 2.1)	47.1 (45.3, 49.0)	NR	20.1 (14.4, 25.9)	19.6 (5.8, 29.3)
HPV51	405	0.8 (0.2, 2.3)	2.6 (1.4, 4.8)	6.1 (4.0, 9.2)	3.4 (2.4, 4.8)	44.9 (43.1, 46.8)	NR	19.1 (15.9, 22.4)	18.6 (12.2, 25.0)
HPV52	418	1.2 (0.5, 2.9)	3.5 (2.1, 5.9)	5.7 (3.7, 8.6)	2.8 (2.0, 4.1)	45.2 (43.1, 47.3)	NR	16.4 (12.6, 20.3)	14.0 (8.5, 19.7)
HPV53	419	1.2 (0.5, 2.9)	4.1 (2.5, 6.6)	7.8 (5.4, 11.1)	3.5 (2.5, 4.8)	45.7 (44.5, 46.9)	NR	15.4 (12.6, 18.3)	13.1 (9.7, 16.9)
HPV56	432	0.9 (0.4, 2.5)	2.7 (1.5, 4.8)	5.4 (3.5, 8.3)	2.2 (1.4, 3.3)	46.3 (44.5, 48.2)	NR	14.9 (11.0, 18.7)	13.5 (9.4, 16.3)
HPV58	431	0.5 (0.1, 1.9)	1.7 (0.8, 3.6)	2.9 (1.6, 5.3)	1.4 (0.8, 2.3)	47.8 (47.0, 48.6)	NR	16.2 (11.5, 20.8)	14.0 (7.1, 22.8)
HPV59	426	1.0 (0.4, 2.6)	1.5 (0.7, 3.3)	4.8 (3.0, 7.7)	2.2 (1.5, 3.3)	46.6 (45.3, 48.0)	NR	17.8 (14.3, 21.4)	17.2 (12.6, 21.5)
HPV66	426	2.2 (1.1, 4.1)	4.4 (2.8, 7.0)	11.4 (8.5, 15.3)	4.7 (3.5, 6.2)	43.6 (41.5, 45.6)	NR	15.9 (13.3, 18.4)	16.6 (11.7, 18.4)
HPV67	427	1.2 (0.5, 2.9)	3.2 (1.9, 5.5)	7.0 (4.8, 10.2)	2.9 (2.0, 4.2)	46.1 (44.9, 47.3)	NR	14.3 (11.4, 17.2)	13.1 (9.4, 17.5)
HPV68	440	0.0[e]	0.7 (0.2, 2.2)	1.4 (0.6, 3.3)	0.5 (0.2, 1.2)	48.9 (48.4, 49.3)	NR	14.8 (8.3, 21.3)	7.4 (6.6, NR)
HPV69[g]	453	0.0	0.0	0.0	0.0	--	NR	--	--
HPV70	450	0.0[e]	0.5 (0.1, 1.9)	1.1 (0.4, 2.9)	0.5 (0.2, 1.2)	48.8 (48.3, 49.3)	NR	18.2 (11.4, 25.0)	13.7 (7.6, NR)
HPV73	435	1.4 (0.6, 3.1)	2.7 (1.5, 4.8)	6.0 (4.0, 9.0)	2.5 (1.7, 3.6)	46.3 (44.8, 47.8)	NR	13.8 (10.4, 17.2)	12.3 (7.0, 15.5)
HPV82	441	0.7 (0.2, 2.1)	1.4 (0.7, 3.2)	2.3 (1.2, 4.4)	0.9 (0.5, 1.7)	48.5 (47.9, 49.1)	NR	11.8 (7.4, 16.1)	9.5 (4.1, 16.8)
Any Woman-Level	233	4.8 (2.7, 8.4)	14.3 (10.3, 19.6)	32.4 (26.4, 39.4)	17.0 (13.7, 20.9)	32.3 (29.6, 35.0)	36.6 (30.8, NR)[h]	16.7 (14.8, 18.6)	14.2 (12.2, 18.4)
Any HPV-Level[f]	9,511	0.7 (0.5, 0.9)	1.7 (1.4, 2.1)	3.8 (3.2, 4.5)	1.7 (1.5, 2.0)	47.2 (45.1, 47.6)	NR	16.5 (15.2, 17.8)	14.5 (12.9, 16.9)
Subgenus 3									
HPV61	443	0.9 (0.4, 2.5)	1.9 (1.0, 3.8)	4.9 (3.1, 7.7)	2.1 (1.4, 3.2)	47.1 (46.1, 48.0)	NR	17.2 (13.7, 20.8)	20.2 (10.6, 21.8)
HPV62	416	1.5 (0.7, 3.2)	4.3 (2.7, 6.9)	8.4 (5.9, 11.8)	3.6 (2.6, 5.0)	43.9 (41.6, 46.3)	NR	15.3 (11.9, 18.6)	12.0 (7.1, 17.0)
HPV71[g]	451	0.0	0.0	0.0	0.0	--	NR	--	--
HPV72[g]	451	0.0	0.0	0.0	0.0	--	NR	--	--
HPV81	446	0.0[e]	0.5 (0.1, 1.9)	0.8 (0.3, 2.5)	0.4 (0.2, 1.1)	48.9 (48.3, 49.4)	NR	20.2 (10.7, 29.7)	22.8 (7.1, NR)
HPV83	444	0.5 (0.1, 1.8)	1.0 (0.4, 2.5)	1.5 (0.7, 3.3)	0.6 (0.3, 1.3)	48.8 (48.3, 49.3)	NR	11.9 (6.7, 17.1)	10.6 (4.3, 19.4)
HPV84	413	2.0 (1.0, 3.9)	5.6 (3.8, 8.4)	9.2 (6.6, 12.6)	4.8 (3.6, 6.3)	43.4 (41.5, 45.3)	NR	16.1 (13.1, 19.0)	13.1 (10.1, 16.4)

HPV89	405	2.8 (1.5, 4.9)	6.0 (4.0, 8.9)	12.5 (9.5, 16.5)	5.5 (4.2, 7.2)	43.6 (42.1, 45.1)	NR	15.1 (12.7, 17.5)	13.8 (9.8, 18.2)
Any Woman-Level	336	5.4 (3.5, 8.5)	13.3 (10.0, 17.5)	24.4 (19.9, 29.7)	12.4 (10.1, 15.1)	35.6 (33.1, 38.1)	40.5 (38.4, NR)[h]	15.5 (13.5, 17.6)	12.6 (10.1, 15.5)
Any HPV-Level[f]	3,469	0.9 (0.6, 1.3)	2.3 (1.7, 3.0)	4.5 (3.7, 5.3)	2.0 (1.7, 2.4)	46.8 (44.5, 47.3)	NR	15.7 (14.1, 17.4)	13.1 (11.5, 15.6)
All 36 Types									
Any Woman-Level	192	4.7 (2.5, 8.9)	16.6 (12.0, 22.8)	40.4 (33.4, 48.4)	20.0 (16.1, 24.9)	30.9 (27.9, 33.9)	32.1 (25.1, NR)[h]	15.4 (13.7, 17.2)	13.1 (12.2, 17.0)
Any HPV-Level[f]	15,598	0.8 (0.6, 1.0)	1.9 (1.6, 2.3)	4.1 (3.6, 4.8)	1.9 (1.7, 2.2)	47.0 (45.0, 47.3)	NR	16.6 (15.5, 17.7)	14.9 (13.1, 16.9)

Abbreviations: CI, confidence interval; HPV, human papillomavirus; NR, not reached.

-- indicates an insufficient number of women were at risk (i.e., 0) or experienced the outcome (i.e., 0 or 1) to estimate this value.

[a] Sample size does not apply to conditional mean/median; sample size for conditional statistics is the number of single detections.

[b] Rate per 1000 woman-months, excepting HPV-level analyses of grouped types, which are provided as rate per 1000 infection-months.

[c] Time to detection including women/types that were censored. Actuarial means were found to be unreliable estimates of average time to detection due to right-censoring.

[d] Time to detection conditional on event of interest (i.e., time to detection restricted to women/types that had a single detection during the study).

[e] HPV type was not detected by this time point among women included in this analysis.

[f] 95% CIs for cumulative detection estimates generated using bootstrap resampling of woman-clusters. 95% CIs for detection rate per 1000 infection-months estimated via woman-clustered jackknife. 95% CIs for actuarial and conditional mean time to detection determined by woman-cluster resampling bootstrap. 95% CIs for actuarial and conditional median time to detection affixed by the times at which each (woman-clustered bootstrap-based) 95% CI bound of the actuarial and conditional survival functions (respectively) reached or fell below 50%.

[g] HPV type was never detected among women included in this analysis.

[h] One bound of the survival function's 95% CI never reached or fell below 50%.

M1-Table 3. Liberal clearance of infection present at baseline for individual HPV types, grouped types at the woman-level, and grouped types at the HPV-level, by subgenus.

	n[a]	Percent of Infection Uncleared, % (95% CI)			Clearance	Time (months) to Clearance (95% CI)			
		6 Months	12 Months	24 Months	Rate[b] (95% CI)	Actuarial Mean[c]	Actuarial Median[c]	Conditional Mean[d]	Conditional Median[d]
Subgenus 1									
HPV6	18	59.3 (33.0, 78.1)	35.6 (14.6, 57.3)	29.6 (10.8, 51.4)	61.6 (35.8, 106.2)	13.7 (8.7, 18.7)	10.6 (5.2, NR)[e]	8.8 (5.1, 12.5)	5.9 (4.6, 11.3)
HPV11	2	NR	NR	NR	228.9 (57.2, 915.0)	4.4 (2.2, 6.5)	2.8 (2.8, NR)[e]	4.4 (2.2, 6.5)	2.8 (2.8, NR)[e]
HPV40	11	61.4 (26.6, 83.5)	40.9 (12.7, 67.9)	13.6 (0.8, 44.0)	74.5 (37.3, 148.9)	11.3 (6.5, 16.1)	8.0 (4.7, 21.4)	8.5 (4.6, 12.3)	5.2 (3.0, 12.6)
HPV42	34	82.0 (64.1, 91.5)	48.0 (29.4, 64.3)	23.0 (9.1, 40.6)	59.3 (39.7, 88.4)	15.0 (11.1, 18.8)	11.7 (7.8, 12.6)	11.1 (8.1, 14.1)	8.0 (7.1, 12.2)
HPV44	8	50.0 (15.2, 77.5)	50.0 (15.2, 77.5)	25.0 (3.7, 55.8)	61.2 (29.2, 128.3)	15.3 (6.5, 24.0)	5.8 (4.4, NR)[e]	12.3 (4.4, 20.2)	5.8 (4.4, 16.3)
HPV54	27	81.5 (61.1, 91.8)	46.9 (27.2, 64.4)	9.5 (1.7, 25.8)	71.4 (47.0, 108.5)	12.3 (9.9, 14.7)	11.5 (8.5, 14.5)	10.5 (8.7, 12.3)	9.9 (7.6, 12.5)
All Woman-Level	86	72.5 (61.6, 80.8)	48.2 (36.8, 58.6)	24.6 (15.3, 35.0)	56.6 (44.0, 72.7)	15.6 (13.0, 18.2)	11.5 (8.5, 13.5)	10.3 (8.5, 12.0)	8.1 (5.9, 10.6)
Any HPV-Level[f]	100	71.3 (60.7, 80.1)	43.7 (33.8, 52.7)	19.2 (10.5, 26.8)	65.8 (53.9, 80.3)	13.9 (11.6, 16.1)	10.6 (8.1, 12.5)	10.2 (8.7, 11.7)	8.0 (7.4, 10.6)
Subgenus 2									
HPV16	79	84.3 (74.0, 90.8)	63.5 (51.4, 73.3)	33.0 (21.8, 44.6)	39.3 (29.5, 52.3)	19.4 (16.5, 22.3)	16.1 (12.3, 19.3)	11.3 (9.7, 13.0)	10.1 (8.5, 13.7)
HPV18	16	68.8 (40.5, 85.6)	43.8 (19.8, 65.6)	16.7 (3.2, 39.3)	73.0 (43.2, 123.2)	12.5 (8.9, 16.2)	11.7 (5.2, 15.9)	10.8 (7.6, 14.0)	11.7 (5.1, 12.4)
HPV26	0	--	--	--	--	--	--	--	--
HPV31	23	90.9 (68.1, 97.6)	67.0 (42.9, 82.7)	19.1 (6.0, 37.9)	60.9 (38.8, 95.5)	14.8 (11.2, 18.4)	12.6 (8.2, 14.1)	13.1 (9.9, 16.2)	12.2 (6.9, 13.7)
HPV33	5	60.0 (12.6, 88.2)	NR	NR	89.4 (28.8, 277.3)	7.2 (4.7, 9.7)	7.6 (4.1, NR)[e]	5.3 (3.6, 7.1)	4.3 (4.1, NR)[e]
HPV34	3	100.0[g]	33.3 (0.9, 77.4)	NR	107.4 (34.6, 333.1)	9.3 (5.5, 13.1)	7.3 (6.7, NR)[e]	9.3 (5.5, 13.1)	7.3 (6.7, NR)[e]
HPV35	3	100.0[g]	66.7 (5.4, 94.5)	NR	43.1 (10.8, 172.5)	15.7 (8.1, 23.3)	20.4 (6.2, NR)[e]	13.3 (3.5, 23.2)	6.2 (6.2, NR)[e]
HPV39	32	79.7 (60.3, 90.3)	55.5 (35.9, 71.2)	7.5 (1.3, 21.1)	65.7 (44.7, 96.5)	13.4 (11.1, 15.8)	12.8 (7.8, 17.7)	12.3 (10.1, 14.4)	12.0 (6.9, 15.8)
HPV45	8	60.0 (19.6, 85.2)	30.0 (4.4, 62.8)	NR	100.0 (47.7, 209.8)	9.4 (6.4, 12.4)	8.3 (5.5, 12.6)	9.2 (6.2, 12.2)	8.3 (5.5, 12.6)
HPV51	48	86.7 (72.7, 93.8)	56.2 (39.5, 69.9)	18.8 (7.3, 34.5)	53.1 (37.6, 75.2)	15.5 (12.8, 18.2)	14.7 (11.0, 18.4)	12.8 (10.5, 15.1)	11.6 (7.0, 14.9)
HPV52	35	72.8 (54.2, 84.8)	45.9 (27.9, 62.2)	13.4 (3.6, 29.6)	66.2 (45.1, 97.2)	13.1 (10.2, 16.1)	8.7 (6.9, 17.7)	10.6 (8.1, 13.2)	7.4 (5.1, 15.6)
HPV53	34	90.7 (73.9, 96.9)	61.2 (41.9, 75.9)	31.7 (15.8, 49.0)	47.2 (31.9, 69.9)	18.5 (14.8, 22.1)	19.1 (9.7, 22.9)	15.7 (12.3, 19.1)	13.7 (8.7, 20.4)
HPV56	21	85.7 (62.0, 95.2)	48.3 (24.7, 68.5)	9.2 (0.6, 32.4)	59.5 (35.9, 98.7)	14.3 (9.3, 19.3)	11.5 (7.8, 20.2)	10.3 (7.5, 13.1)	8.5 (5.1, 12.2)
HPV58	22	90.4 (66.8, 97.5)	62.2 (36.4, 80.0)	15.5 (2.8, 37.9)	50.8 (30.1, 85.8)	15.7 (11.6, 19.8)	12.9 (8.7, 21.1)	12.0 (9.1, 15.0)	9.9 (6.5, 15.6)
HPV59	27	81.5 (61.1, 91.8)	36.7 (18.7, 54.9)	NR	82.6 (55.4, 123.2)	11.3 (9.2, 13.3)	9.5 (8.0, 14.7)	10.7 (8.7, 12.6)	9.4 (7.7, 12.4)
HPV66	27	73.7 (52.6, 86.5)	41.0 (22.0, 59.1)	4.1 (0.3, 17.3)	89.0 (60.2, 131.8)	10.9 (8.7, 13.2)	8.5 (7.5, 14.3)	10.8 (8.5, 13.1)	8.5 (7.5, 14.3)
HPV67	26	73.1 (51.7, 86.2)	38.5 (20.4, 56.3)	NR	93.1 (63.4, 136.7)	10.7 (8.5, 13.0)	8.5 (6.6, 13.1)	10.7 (8.5, 13.0)	8.5 (6.6, 13.1)
HPV68	13	91.7 (53.9, 98.8)	66.7 (33.7, 86.0)	33.3 (10.3, 58.8)	34.8 (17.4, 69.6)	19.9 (14.3, 25.5)	19.5 (8.5, NR)[e]	13.8 (9.7, 18.0)	11.7 (3.7, 19.7)
HPV69	0	--	--	--	--	--	--	--	--
HPV70	3	66.7 (5.4, 94.5)	66.7 (5.4, 94.5)	33.3 (0.9, 77.4)	55.4 (17.9, 171.8)	18.0 (5.4, 30.7)	17.4 (4.7, NR)[e]	18.0 (5.4, 30.7)	17.4 (4.7, NR)[e]
HPV73	18	66.7 (40.4, 83.4)	24.4 (7.7, 46.1)	12.2 (2.1, 32.1)	86.1 (52.8, 140.6)	10.7 (7.4, 13.9)	9.8 (5.0, 12.0)	9.3 (6.7, 12.0)	9.7 (4.9, 11.7)
HPV82	12	50.0 (20.9, 73.6)	8.3 (0.5, 31.1)	NR	140.3 (79.7, 247.0)	7.1 (4.8, 9.5)	5.5 (3.1, 9.3)	7.1 (4.8, 9.5)	5.5 (3.1, 9.3)
All Woman-Level	220	91.5 (86.9, 94.6)	78.2 (71.8, 83.3)	48.0 (40.1, 55.4)	27.4 (22.6, 33.2)	24.7 (22.6, 26.8)	23.7 (20.0, 26.1)	14.6 (13.1, 16.1)	14.2 (11.7, 15.8)
Any HPV-Level[f]	455	80.5 (75.7, 84.8)	50.8 (45.8, 55.6)	16.3 (12.3, 20.2)	60.5 (55.4, 66.2)	14.9 (13.9, 16.0)	12.1 (10.8, 13.2)	11.5 (10.8, 12.2)	9.9 (8.7, 11.0)
Subgenus 3									
HPV61	10	77.8 (36.5, 93.9)	55.6 (20.4, 80.5)	44.4 (13.6, 71.9)	37.7 (16.9, 84.0)	18.7 (10.5, 26.9)	16.2 (3.9, NR)[e]	11.6 (5.3, 17.9)	7.9 (3.9, NR)[e]
HPV62	37	88.6 (72.4, 95.6)	61.6 (43.1, 75.6)	37.0 (20.4, 53.8)	41.5 (28.0, 61.4)	19.3 (15.6, 23.0)	19.2 (8.8, 25.0)	15.1 (11.7, 18.6)	11.6 (8.2, 19.5)
HPV71	2	100.0[g]	NR	NR	122.0 (30.5, 487.8)	8.2 (5.8, 10.6)	6.5 (6.5, NR)[e]	8.2 (5.8, 10.6)	6.5 (6.5, NR)[e]
HPV72[h]	2	100.0	100.0	100.0	0.0	--	NR	--	--
HPV81	7	83.3 (27.3, 97.5)	66.7 (19.5, 90.4)	NR	68.9 (28.7, 165.5)	11.2 (8.2, 14.2)	12.8 (5.8, NR)[e]	10.5 (7.3, 13.7)	12.8 (5.8, NR)[e]
HPV83	9	88.9 (43.3, 98.4)	64.8 (25.3, 87.2)	48.6 (12.8, 77.6)	35.9 (14.9, 86.2)	20.4 (11.3, 29.5)	12.6 (5.5, NR)[e]	12.4 (4.4, 20.4)	7.9 (5.5, NR)[e]
HPV84	40	79.4 (63.0, 89.1)	28.9 (15.2, 44.1)	10.4 (2.9, 23.6)	86.9 (61.8, 122.2)	10.5 (8.1, 12.8)	7.5 (6.4, 10.4)	8.7 (7.0, 10.4)	7.3 (6.2, 8.5)

HPV89	48	74.8 (60.0, 84.9)	38.4 (24.7, 51.9)	8.2 (2.2, 19.4)	78.7 (58.4, 106.1)	12.3 (9.7, 15.0)	9.4 (7.8, 12.1)	11.0 (8.7, 13.3)	8.9 (6.7, 11.3)
All Woman-Level	117	82.2 (73.8, 88.2)	57.1 (47.1, 65.9)	34.0 (24.6, 43.6)	45.8 (36.6, 57.4)	18.4 (15.8, 21.0)	14.2 (11.3, 17.8)	12.0 (10.2, 13.9)	9.3 (6.8, 12.1)
Any HPV-Level[f]	155	81.4 (73.9, 86.7)	45.1 (36.1, 54.0)	20.9 (13.6, 29.6)	61.0 (50.6, 73.3)	14.9 (12.7, 17.1)	10.4 (8.5, 13.1)	11.3 (10.0, 12.6)	8.5 (7.5, 9.7)
All 36 Types									
All Woman-Level	261	91.7 (87.5, 94.5)	80.1 (74.5, 84.6)	57.3 (50.2, 63.8)	23.6 (19.6, 28.4)	26.0 (24.0, 27.9)	27.0 (25.0, 32.7)	14.8 (13.2, 16.4)	14.0 (11.6, 15.6)
Any HPV-Level[f]	710	79.4 (74.4, 82.8)	48.6 (44.1, 52.6)	17.7 (13.9, 21.2)	61.3 (56.2, 66.9)	14.8 (13.7, 15.8)	11.7 (10.3, 12.6)	11.3 (10.6, 11.9)	9.3 (8.5, 10.2)

Abbreviations: CI, confidence interval; HPV, human papillomavirus; NR, not reached.

-- indicates an insufficient number of women were at risk (i.e., 0) or experienced the outcome (i.e., 0 or 1) to estimate this value.

[a] Sample size does not apply to conditional mean/median; sample size for conditional statistics is the number of liberal clearances.

[b] Rate per 1000 woman-months, excepting HPV-level analyses of grouped types, which are provided as rate per 1000 infection-months.

[c] Time to clearance including women/infections that were censored.

[d] Time to clearance conditional on event of interest (i.e., time to clearance restricted to women/infections that had a liberal clearance during the study).

[e] One bound of the survival function's 95% CI never reached or fell below 50%.

[f] 95% CIs for uncleared infection estimates generated using bootstrap resampling of woman-clusters. 95% CIs for clearance rate per 1000 infection-months estimated via woman-clustered jackknife. 95% CIs for actuarial and conditional mean time to clearance determined by woman-cluster resampling bootstrap. 95% CIs for actuarial and conditional median time to clearance affixed by the times at which each (woman-clustered bootstrap-based) 95% CI bound of the actuarial and conditional survival functions (respectively) reached or fell below 50%.

[g] HPV type was not cleared by this time point among women included in this analysis.

[h] HPV type was never cleared among women included in this analysis.

M1-Table 4. Liberal clearance of incident infection for individual HPV types, grouped types at the woman-level, and grouped types at the HPV-level, by subgenus.

	n[a]	Percent of Infection Uncleared, % (95% CI)			Clearance	Time (months) to Clearance (95% CI)			
		6 Months	12 Months	24 Months	Rate[b] (95% CI)	Actuarial Mean[c]	Actuarial Median[c]	Conditional Mean[d]	Conditional Median[d]
Subgenus 1									
HPV6	32	79.4 (59.8, 90.2)	35.2 (16.8, 54.2)	NR	66.4 (41.8, 105.3)	12.1 (9.3, 14.8)	9.3 (7.6, 12.8)	8.4 (6.5, 10.2)	7.6 (5.3, 9.3)
HPV11	1	NR	NR	NR	172.9 (24.4, 1,227.7)	--	NR	--	NR
HPV40	14	85.7 (53.9, 96.2)	47.6 (20.3, 70.8)	NR	73.9 (40.9, 133.4)	11.5 (9.1, 13.8)	10.2 (6.1, 16.2)	10.5 (7.9, 13.0)	9.9 (5.2, 15.1)
HPV42	34	82.0 (64.3, 91.5)	52.1 (33.3, 67.9)	23.1 (9.1, 40.9)	55.1 (36.3, 83.7)	14.7 (11.4, 18.0)	12.4 (8.6, 16.0)	9.7 (8.0, 11.4)	8.6 (5.7, 12.4)
HPV44	4	100.0[e]	33.3 (0.9, 77.4)	NR	74.2 (23.9, 230.2)	11.3 (5.7, 16.9)	8.5 (7.2, NR)[f]	11.3 (5.7, 16.9)	8.5 (7.2, NR)[f]
HPV54	19	89.5 (64.1, 97.3)	44.2 (17.5, 68.2)	22.1 (1.6, 57.5)	50.6 (27.2, 94.0)	15.0 (10.8, 19.3)	10.6 (7.9, NR)[f]	10.8 (6.5, 15.1)	8.0 (3.0, 10.6)
All Woman-Level	69	86.8 (76.1, 92.9)	55.0 (40.9, 67.1)	19.9 (6.5, 38.6)	45.6 (32.7, 63.5)	15.6 (13.0, 18.2)	14.3 (9.9, 17.6)	9.8 (8.2, 11.4)	8.7 (7.3, 10.0)
Any HPV-Level[g]	104	83.5 (74.8, 89.4)	52.3 (41.1, 62.1)	34.7 (24.2, 44.8)	43.4 (33.6, 56.4)	18.5 (15.4, 21.1)	13.1 (9.9, 17.6)	9.6 (8.6, 10.9)	8.5 (7.6, 9.9)
Subgenus 2									
HPV16	22	83.3 (56.8, 94.3)	67.3 (36.6, 85.6)	NR	36.5 (17.4, 76.6)	14.0 (10.7, 17.3)	15.3 (6.7, NR)[f]	8.5 (5.7, 11.4)	6.7 (4.8, 13.0)
HPV18	10	80.0 (40.9, 94.6)	50.0 (18.4, 75.3)	50.0 (18.4, 75.3)	34.7 (14.5, 83.4)	18.6 (11.4, 25.8)	10.2 (4.6, NR)[f]	7.1 (5.4, 8.8)	7.4 (4.6, NR)[f]
HPV26	0	--	--	--	--	--	--	--	--
HPV31	19	78.0 (51.5, 91.1)	36.0 (13.6, 59.3)	NR	69.1 (39.2, 121.7)	11.3 (8.4, 14.1)	9.8 (6.8, NR)[f]	8.6 (6.2, 10.9)	8.0 (4.6, 10.0)
HPV33	4	50.0 (5.8, 84.5)	NR	NR	153.1 (57.5, 408.0)	6.5 (4.5, 8.5)	5.5 (3.7, NR)[f]	6.5 (4.5, 8.5)	5.5 (3.7, NR)[f]
HPV34	2	50.0 (0.6, 91.0)	NR	NR	168.6 (42.2, 674.2)	5.9 (5.8, 6.0)	5.8 (5.8, NR)[f]	5.9 (5.8, 6.0)	5.8 (5.8, NR)[f]
HPV35	4	75.0 (12.8, 96.1)	75.0 (12.8, 96.1)	NR	55.3 (17.8, 171.5)	16.6 (9.7, 23.5)	18.5 (5.0, NR)[f]	15.4 (6.9, 23.8)	18.5 (5.0, NR)[f]
HPV39	19	89.5 (64.1, 97.3)	57.0 (29.7, 77.1)	19.0 (3.2, 44.9)	54.0 (29.9, 97.5)	14.1 (9.5, 18.7)	12.6 (8.1, 14.8)	9.6 (7.6, 11.6)	8.5 (5.6, 12.6)
HPV45	8	75.0 (31.5, 93.1)	20.8 (1.0, 58.6)	NR	90.7 (40.8, 201.9)	9.4 (5.3, 13.4)	7.6 (4.7, NR)[f]	8.6 (4.9, 12.3)	6.2 (4.7, NR)[f]
HPV51	23	86.7 (64.3, 95.5)	47.2 (23.4, 67.8)	12.6 (1.0, 39.3)	61.8 (37.3, 102.6)	13.7 (9.9, 17.5)	11.3 (6.3, 16.3)	11.1 (7.6, 14.7)	9.4 (4.9, 15.1)
HPV52	19	89.2 (63.2, 97.2)	50.2 (26.1, 70.2)	13.7 (1.1, 41.7)	59.1 (34.3, 101.8)	13.6 (9.9, 17.3)	12.6 (6.8, 23.0)	10.0 (7.1, 12.8)	9.0 (6.2, 12.6)
HPV53	25	78.7 (56.1, 90.6)	64.1 (40.5, 80.3)	NR	56.0 (33.2, 94.5)	13.7 (10.5, 16.9)	14.1 (6.4, 18.4)	10.0 (6.8, 13.3)	6.4 (3.7, 14.9)
HPV56	16	85.7 (53.9, 96.2)	39.6 (12.8, 65.9)	NR	70.4 (37.9, 130.8)	10.7 (8.2, 13.2)	8.6 (6.3, 15.5)	9.7 (7.2, 12.1)	8.2 (5.3, 12.7)
HPV58	13	92.3 (56.6, 98.9)	92.3 (56.6, 98.9)	20.2 (0.9, 58.0)	31.8 (14.3, 70.7)	21.5 (15.4, 27.6)	22.3 (12.2, NR)[f]	19.1 (11.6, 26.5)	18.2 (4.5, NR)[f]
HPV59	18	70.8 (43.5, 86.7)	27.0 (6.9, 52.7)	27.0 (6.9, 52.7)	67.5 (37.4, 121.9)	13.7 (7.8, 19.5)	9.4 (5.1, NR)[f]	9.1 (4.8, 13.3)	7.1 (4.6, 9.9)
HPV66	35	73.2 (54.8, 85.1)	33.1 (16.6, 50.6)	NR	91.8 (63.0, 133.9)	9.7 (7.9, 11.4)	8.8 (6.2, 13.1)	8.7 (7.0, 10.4)	7.6 (5.3, 10.2)
HPV67	25	88.0 (67.3, 96.0)	37.8 (19.2, 56.3)	NR	80.4 (52.4, 123.3)	10.9 (9.0, 12.8)	8.5 (7.2, 14.0)	9.8 (8.0, 11.7)	8.3 (6.9, 11.3)
HPV68	6	80.0 (20.4, 96.9)	26.7 (1.0, 68.6)	NR	57.7 (18.6, 179.0)	11.0 (8.0, 14.0)	11.5 (5.6, NR)[f]	9.2 (6.2, 12.1)	10.5 (5.6, NR)[f]
HPV69	0	--	--	--	--	--	--	--	--
HPV70	5	80.0 (20.4, 96.9)	40.0 (5.2, 75.3)	40.0 (5.2, 75.3)	65.6 (24.6, 174.7)	14.4 (5.8, 23.0)	7.3 (5.6, NR)[f]	11.4 (2.8, 19.9)	6.2 (5.6, NR)[f]
HPV73	21	81.0 (56.9, 92.4)	40.7 (18.7, 61.8)	NR	79.7 (48.8, 130.1)	11.0 (8.9, 13.2)	9.6 (7.5, 16.1)	10.0 (7.8, 12.3)	8.8 (5.3, 15.8)
HPV82	9	77.8 (36.5, 93.9)	22.2 (3.4, 51.3)	NR	81.2 (38.7, 170.3)	9.6 (7.1, 12.1)	9.3 (3.8, NR)[f]	7.8 (6.3, 9.4)	8.9 (3.8, 9.4)
All Woman-Level	68	87.7 (76.8, 93.6)	57.1 (42.8, 69.2)	18.4 (6.3, 35.5)	47.2 (34.1, 65.5)	17.2 (13.4, 21.0)	13.5 (9.4, 18.5)	10.1 (8.4, 11.9)	8.3 (6.4, 11.3)
Any HPV-Level[g]	303	81.7 (76.1, 86.2)	51.9 (45.0, 57.7)	31.0 (24.1, 36.5)	47.1 (39.9, 55.5)	19.1 (15.9, 21.2)	12.7 (9.4, 15.1)	9.7 (8.9, 10.6)	8.1 (7.3, 8.9)
Subgenus 3									
HPV61	16	81.3 (52.5, 93.5)	48.8 (17.1, 74.7)	NR	42.8 (20.4, 89.9)	14.5 (10.0, 18.9)	11.9 (7.9, NR)[f]	8.0 (5.3, 10.8)	7.9 (3.0, 11.9)
HPV62	25	79.5 (57.5, 90.9)	46.0 (24.3, 65.3)	12.6 (1.1, 38.9)	65.7 (40.8, 105.7)	13.1 (9.4, 16.7)	11.7 (6.8, 14.4)	10.4 (7.4, 13.3)	8.2 (5.7, 12.2)
HPV71	0	--	--	--	--	--	--	--	--
HPV72	0	--	--	--	--	--	--	--	--
HPV81	2	100.0[e]	100.0[e]	NR	44.8 (6.3, 318.2)	--	12.2 (NR, NR)[f]	--	NR
HPV83	7	100.0[e]	17.1 (0.8, 52.6)	NR	82.5 (34.4, 198.3)	9.1 (7.4, 10.8)	8.8 (6.2, NR)[f]	8.2 (7.0, 9.5)	8.5 (6.2, NR)[f]
HPV84	34	63.9 (45.2, 77.7)	37.0 (19.7, 54.4)	14.8 (4.1, 31.9)	79.2 (53.5, 117.1)	11.5 (8.6, 14.5)	8.5 (5.6, 15.1)	8.8 (6.4, 11.1)	6.1 (4.6, 9.9)

HPV89	43	88.0 (73.6, 94.8)	51.4 (34.7, 65.8)	20.9 (6.7, 40.5)	57.5 (39.7, 83.3)	14.4 (11.6, 17.2)	12.9 (8.1, 20.1)	11.3 (8.7, 13.9)	8.1 (6.7, 11.3)
All Woman-Level	71	80.1 (68.7, 87.7)	59.1 (45.6, 70.3)	26.7 (13.2, 42.3)	51.0 (37.4, 69.6)	15.3 (12.9, 17.7)	14.4 (10.8, 19.7)	10.4 (8.2, 12.5)	6.8 (5.7, 11.8)
Any HPV-Level[g]	127	80.3 (72.4, 85.6)	50.9 (40.3, 58.8)	35.0 (24.5, 42.0)	46.6 (37.7, 57.7)	17.3 (14.8, 19.4)	12.2 (9.7, 15.1)	9.9 (8.6, 11.4)	8.0 (6.7, 9.6)
All 36 Types									
All Woman-Level	65	93.5 (83.6, 97.5)	74.1 (60.1, 83.9)	39.8 (19.2, 59.7)	25.5 (16.8, 38.7)	24.2 (19.6, 28.9)	22.3 (16.2, NR)[f]	11.1 (8.7, 13.5)	8.7 (6.4, 13.5)
Any HPV-Level[g]	534	81.7 (77.1, 86.0)	51.7 (46.6, 56.4)	32.7 (27.4, 36.8)	46.2 (41.1, 52.0)	19.3 (16.9, 20.8)	12.6 (10.3, 14.8)	9.8 (9.1, 10.5)	8.2 (7.6, 8.8)

Abbreviations: CI, confidence interval; HPV, human papillomavirus; NR, not reached.

-- indicates an insufficient number of women were at risk (i.e., 0) or experienced the outcome (i.e., 0 or 1) to estimate this value.

[a] Sample size does not apply to conditional mean/median; sample size for conditional statistics is the number of liberal clearances.

[b] Rate per 1000 woman-months, excepting HPV-level analyses of grouped types, which are provided as rate per 1000 infection-months.

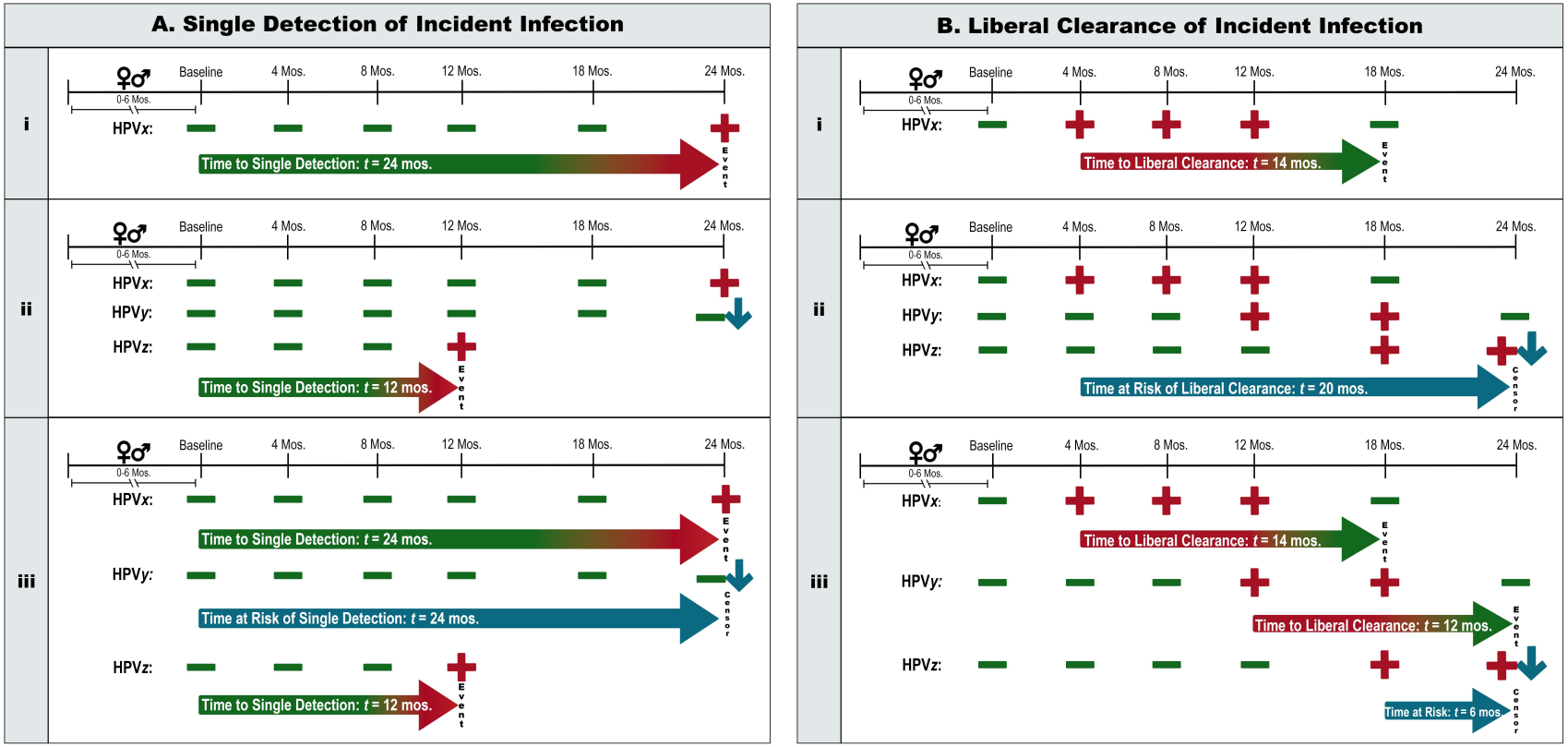
[c] Time to clearance including women/infections that were censored.

[d] Time to clearance conditional on event of interest (i.e., time to clearance restricted to women/infections that had a liberal clearance during the study).

[e] HPV type was not cleared by this time point among women included in this analysis.

[f] Bound(s) of the survival function's 95% CI never reached or fell below 50%.

[g] 95% CIs for uncleared infection estimates generated using bootstrap resampling of woman-clusters. 95% CIs for clearance rate per 1000 infection-months estimated via woman-clustered jackknife. 95% CIs for actuarial and conditional mean time to clearance determined by woman-cluster resampling bootstrap. 95% CIs for actuarial and conditional median time to clearance affixed by the times at which each (woman-clustered bootstrap-based) 95% CI bound of the actuarial and conditional survival functions (respectively) reached or fell below 50%.



Abbreviations: HPV, human papillomavirus; mos., months (1 month = 30.437 days).

M1-Figure 1A. Analytical framework for single detection of incident infection.

i. Woman-level analysis for a given HPV type: Woman A must be negative for HPV*x* at baseline. She has a single detection at 24 months, when she tests positive for HPV*x*.

ii. Woman-level analysis for grouped HPV types *x, y,* and *z*: Woman A must be negative for all three types at baseline. She has a single detection at 12 months, the first time she tests positive for one (or more) types following a visit where she was negative for all three types.

iii. HPV-level analysis for grouped HPV types *x, y,* and *z*: HPV types must be absent at baseline. There will be a single detection each first time woman A tests positive for any type following a visit where she was negative for the same type. HPV*x* and HPV*z* have single detections at 24- and 12-months, respectively; HPV*y* is right-censored (24 months).

M1-Figure 1B. Analytical framework for liberal clearance of incident infection.

i. Woman-level analysis for a given HPV type: Woman B must be negative for HPV*x* at baseline. She later tests positive for HPV*x,* then has a liberal clearance after 14 months have elapsed, when she tests negative for HPV*x.*

ii. Woman-level analysis for grouped HPV types *x, y,* and *z*: Woman B must be negative for all three types at baseline. After testing positive for HPV*x,* she never clears all three asynchronously-detected infections at a single visit. She is right-censored (24 months).

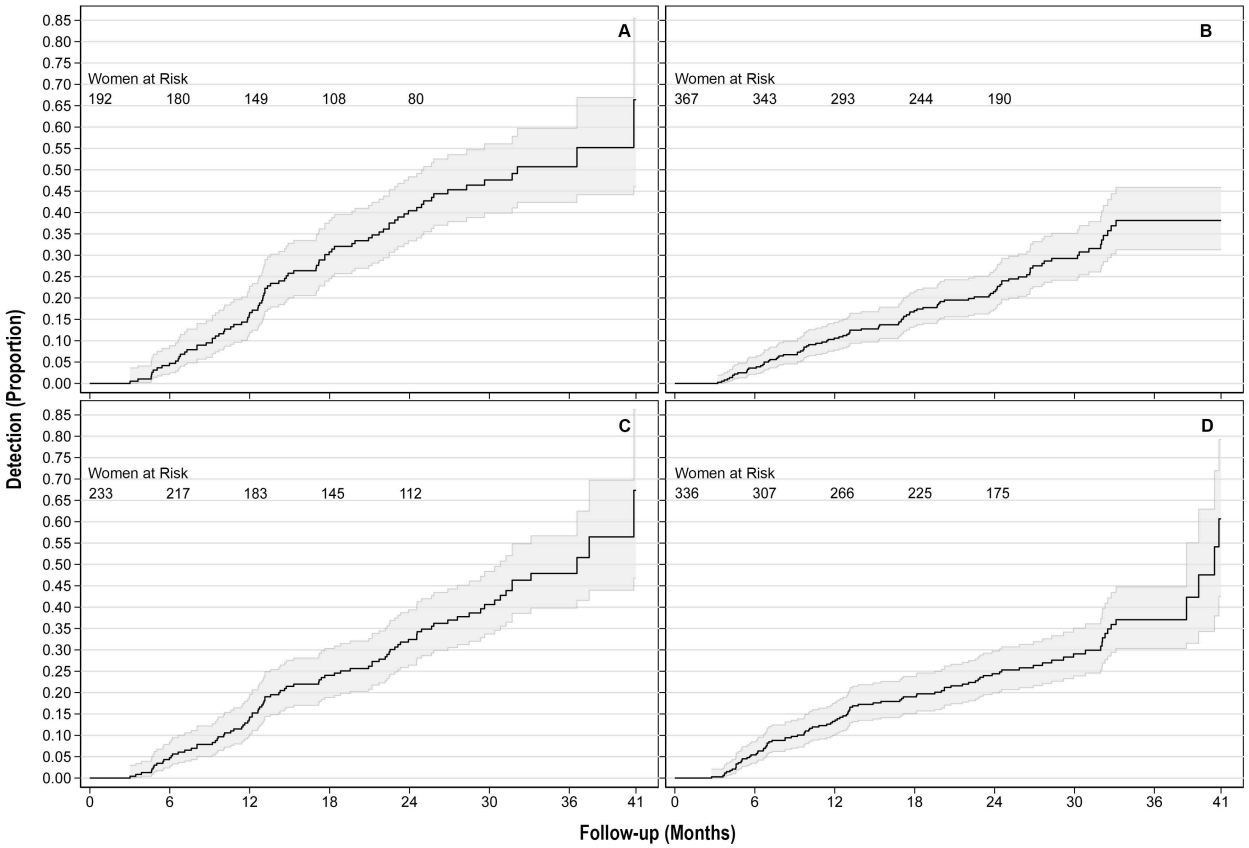
iii. HPV-level analysis for grouped HPV types *x, y,* and *z*: HPV types must be absent at baseline, then detected later in the study. There will be a liberal clearance each first time woman B tests negative for any type following a visit where she was positive for the same type. HPV*x* and HPV*y* have liberal clearances 14- and 12-months post-detection, respectively; HPV*z* is right-censored 6 months after detection.

Symbol Legend:

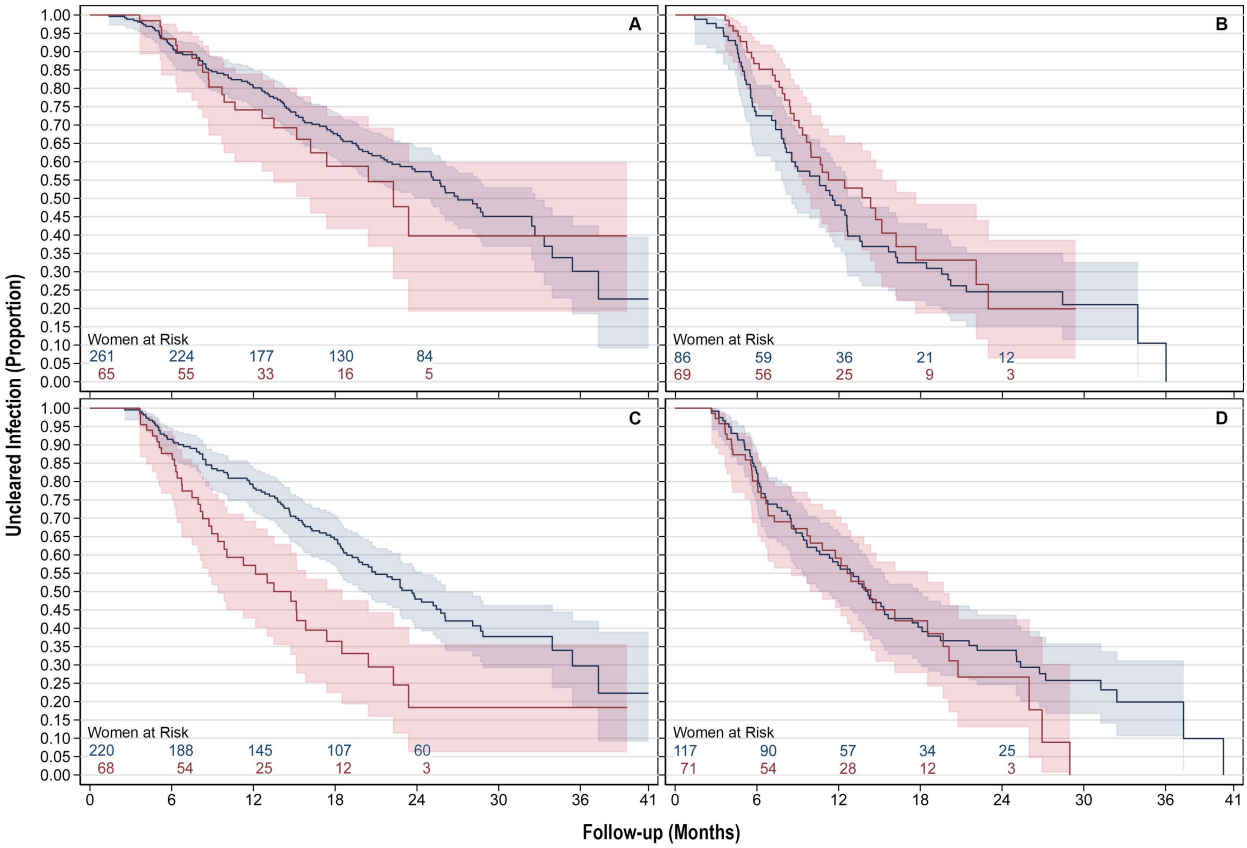
⚥ : Debut of woman's sexual relationship with a male partner occurred 0-6 months pre-baseline.

⬇ : Data are right-censored.

⟹ : Time to discrete event of interest. Gradient arrows indicate that biological infection/clearance occurred at an unknown time before detection/clearance at the arrowhead. Solid blue arrow counts time at risk contributed before censorship at the arrowhead.



M1-Figure 2. Single detection of incident infection with any (A) HPV type(s), (B) subgenus 1, (C) subgenus 2, and (D) subgenus 3 type(s), at the woman-level.



M1-Figure 3. Liberal clearance of all (A) HPV type(s), (B) subgenus 1, (C) subgenus 2, and (D) subgenus 3 type(s) for infections present at baseline (blue) and incident infections (red), at the woman-level.

CHAPTER 4. HPV TRANSMISSION IN FEMALES' SEQUENTIAL MALE PARTNERS

4.1 PREFACE

Chapter 3 provided an in-depth examination of HPV natural history in young women. As molecular HPV testing replaces Pap cytology as the dominant technique for cervical screening,[7] we hope these estimates will be informative for epidemiologists and mathematical modelers undertaking secondary cervical cancer prevention research.

As a couple-based cohort, the HITCH study is equally well-positioned to investigate a phenomenon of interest to primary HPV-related cancer prevention: HPV transmission. A unique property of the HITCH study allowed us to analyze HPV transmission from upstream sexual partnerships (male 1↔female) to downstream sex partners (→male 2). A total of 42 females enrolled in HITCH brought more than one sex partner to the study. In chapter 4, we use HPV genotyping data for 42 "female-linked partnerships" to characterize HPV transmission between sequential heterosexual partnerships. Understanding HPV's ability to transmit across sexual partnerships may have implications for primary HPV-related cancer prevention by informing vaccination targetting. We believe this to be the first such analysis among longitudinal couple-based HPV transmission studies.[26-31,65]

The results of our analysis are presented in Manuscript 2. A later edition of *Epidemiology of genital human papillomavirus infections in sequential male sex partners of young females* was made available as a preprint on medRxiv.org[66] and submitted to *Clinical Microbiology and Infection* (Elsevier) on June 19th, 2023. Portions of this manuscript were presented at the 23rd Annual McGill Biomedical Graduate Conference on March 17th, 2023, a McGill University Department of Oncology seminar on June 1st, 2023, the McGill University Faculty of Medicine and Health Sciences Celebration of Research and Training in Oncology on June 8th, 2023, and the 2023 Canadian Society for Epidemiology and Biostatistics Conference on June 28th, 2023.

4.2 EPIDEMIOLOGY OF GENITAL HUMAN PAPILLOMAVIRUS INFECTIONS IN SEQUENTIAL MALE SEX PARTNERS OF YOUNG FEMALES

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4.2.1 Abstract

Objectives. Couple-based studies have largely considered human papillomavirus (HPV) transmission between current heterosexual partners (male↔female). Using data from young women and their sequential male partners in the HPV Infection and Transmission among Couples through Heterosexual activity (HITCH) study, we analysed HPV transmission from upstream sexual partnerships (male 1↔female) to downstream sex partners (→male 2).

Methods. 42 females enrolled in the HITCH study (2005-2011, Montréal, Canada) brought a male sex partner at baseline (male 1; *n*=42) and another during follow-up (male 2; *n*=42). Female genital samples, collected at 6 visits over 24 months, and male genital samples, collected at 2 visits over 4 months, were tested for 36 HPV types (*n*=1,512 detectable infections). We calculated observed/expected ratios with 95% confidence intervals (CIs) for type-specific HPV concordance between males 1 and 2. Using mixed-effects regression, we estimated odds ratios (ORs) with 95% CIs for male 2 testing positive for the same HPV type as male 1.

Results. Detection of the same HPV type in males 1 and 2 occurred 2.6 times (CI:1.9-3.5) more often than chance. The OR for male 2 positivity was 4.2 (CI:2.5-7.0). Adjusting for the number of times the linking female tested positive for the same HPV type attenuated the relationship between male 1 and 2 positivity, suggesting mediation.

Conclusions. High levels of type-specific HPV concordance between males 1 and 2 suggest HPV is transmissible to subsequent heterosexual partners. HPV positivity in an upstream partnership predicted positivity in a downstream male when the linking female partner was persistently positive.

Keywords: Papillomaviridae, human papillomavirus, sexually transmitted infection, prospective cohort study, couple-based study, concordance, transmission, sexual partnerships, young adults

4.2.2 Introduction

Human papillomavirus (HPV) is the most prevalent sexually transmitted infection (STI), with young adults bearing the principal disease burden [1]. Genital infection with oncogenic HPV types is a necessary cause of cervical cancer and a component cause of other anogenital cancers in males and females [2]. Vaccination prevents HPV infection in the individual and creates population-level herd effects, whereby limiting incident infections in vaccinated individuals prevents transmission to unvaccinated individuals [3].

To date, couple-based studies have focused on HPV concordance and transmission between male and female partners in a current sexual relationship [4-12], estimating the impact of past and concurrent partners on HPV incidence in current sex partners [7, 9-12]. However, to adequately characterize HPV transmission between sequential sexual partnerships, HPV genotyping data for multiple sex partners of the same individual would be required. We performed a post hoc analysis of genital HPV transmission from upstream current sexual partnerships to downstream sex partners (male 1↔female→male 2) in the HPV Infection and Transmission among Couples through Heterosexual activity (HITCH) Cohort Study. We aimed to characterize type-specific HPV concordance and associations between sequential male partners of the same female and identify correlates of HPV types detected in male 1 being detected in male 2.

4.2.3 Methods

i. Study Design

Full details on the HITCH study have been published elsewhere [13]. Briefly, in Montréal, Canada (2005-2011), we enrolled post-secondary females and their male partners within their first

6 months of sexual activity together. By design, self-reported sex determined enrolment; gender data were not collected. During follow-up, some females brought subsequent male partners into the study, forming a female-linked partnership (male 1↔female→male 2). Each participant within the linked partnership completed questionnaires. Females provided vaginal samples at baseline and 5 follow-up visits (4-, 8-, 12-, 18- and 24-months) while males provided scrotal and penile samples at two visits: baseline and, beginning in October 2006, follow-up at 4 months. Couples were asked to refrain from penetrative sex 24 hours before sampling. Females were instructed to collect a vaginal sample using a polyester swab (diagnostic accuracy validated [14]). Nurses collected male epithelial cells using emery exfoliation, collecting separate polyester swab samples of the scrotum and penis (glans, external meatus, coronal sulcus, shaft, and foreskin), a well-validated technique [15]. We tested samples for 36 HPV types using the Linear Array genotyping assay (Roche Molecular Systems), assessing cellularity via β-globin DNA coamplification [16]. Noting a high degree of type-specific HPV co-detection between scrotal and penile samples, we combined an increasing proportion of male genital samples prior to genotyping over time.

The Institutional Review Boards of McGill and Concordia Universities, and the Centre Hospitalier de l'Université de Montreal approved the HITCH study; all participants provided written informed consent.

ii. Statistical Analyses

We treated female-linked partnerships as the units of observation and detectable HPV infections as the units of analysis. We used Cohen's kappa to assess the degree of type-specific HPV positivity agreement between uncombined scrotal and penile samples at each visit, as well as between combined genital samples at baseline and follow-up. Kappa values 0.41-0.60 indicated moderate, 0.61-0.80 indicated substantial, and 0.81-1.00 indicated almost perfect agreement [17].

We combined positivity for each male into a single measure per HPV type (i.e., HPV type x positivity at either/both genital site(s) at either/both visit(s)).

Analyses were performed for any HPV type and by Alphapapillomavirus subgenera. The latter grouped HPV types by tissue tropism, oncogenicity and phylogenetic relatedness, generating groups that included biologically and clinically comparable types. Subgenus 1 includes low oncogenic risk mucosal HPVs 6, 11, 40, 42, 44, and 54; subgenus 2 includes high oncogenic risk mucosal HPVs 16, 18, 26, 31, 33, 34, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73 and 82; and subgenus 3 includes commensal mucocutaneous HPVs 61, 62, 71, 72, 81, 83, 84 and 89 [18, 19]. The ability to detect multiple HPV genotypes in the same genital sample can generate intraparticipant correlation in analyses of grouped HPV types [20]; we used statistical approaches that account for the resultant data clustering (detailed below).

Assuming HPV positivity is independent for males 1 and 2, their expected concordance would be the product of infection prevalence divided by total detectable infections. We calculated observed/expected (O/E) ratios for type-specific HPV concordance between males 1 and 2 with percentile-based 95% confidence intervals (CIs). Bootstrap CIs maintain nominal coverage when a ratio's dividend and divisor are highly correlated [21]. Our H_0: $Observed\ Concordance = Expected\ Concordance$ implies O/E ratio divisor/dividend correlation. Bootstraps for overall and subgenera-specific analyses resampled data by linked-partnership clusters.

We used mixed-effects logistic regression models with random intercepts by linked partnership and an exchangeable correlation structure to estimate odds ratios (ORs) with 95% CIs for male 2 testing positive (outcome) for an HPV type detected in male 1 (exposure) [20]. We selected covariates based on previous investigations of HPV transmission and natural history in the HITCH study [12, 22]. We stratified/adjusted by covariates pertaining to HPV positivity:

number of times the female partner tested positive up to male 2 enrolment; and time between the last available male 1 sample and baseline male 2 sample (< vs ≥median). We also adjusted/stratified by sexual behaviour covariates pertaining to the downstream partnership: male 2 concurrent partners; instances of vaginal sex (< vs ≥median); and frequency of condom use during vaginal sex (≤ vs >75%). Strata cutoffs were defined to optimize the equivalency of detectable infections between strata.

We performed additional analyses to explore the impact of differential male detection opportunities and female cell deposition on our risk estimates. For the former, we adjusted for the sum of male 1 and 2 genital samples provided in each linked partnership. For the latter, given previous findings of male cells in vaginal specimens of HITCH study females, we adjusted and stratified by the time since vaginal sex at male 2 baseline visit (≤ vs >3 days) [23]. Statistical analyses were conducted using Stata SE 17.0.

4.2.4 Results

Of 502 enrolled females, 42 brought a second male partner later in the study, resulting in an observational sample of 42 female-linked partnerships (42 females, 84 males), and an analytical sample of 1,512 detectable HPV infections (M2-Figure 1). The median time between the last available male 1 sample and the baseline male 2 sample was 10.2 months (interquartile range: 6.4-18.4 months; M2-Figure S1 presents the distribution of time elapsed). Demographic and lifestyle covariates were similar between partners (M2-Table 1). Males were, on average, older at baseline and had more lifetime vaginal sex partners compared to females. Male 2 was generally older and had more past vaginal sex partners compared to male 1. M2-Table S1 shows moderate to strong agreement between uncombined genital samples (kappa: 0.47-1) and between combined genital

samples at both male visits (0.55-0.75), which justified combining baseline and follow-up penile and scrotal results.

Overall, concordance for any HPV infection between males 1 and 2 was observed 2.6, CI:1.9-3.5 times more often than expected (M2-Table 2). About a quarter (29/120; 24.2%) of HPV infections detected in male 1 were also detected in male 2. M2-Figure S2 shows the expected type-specific concordance distribution.

As shown in M2-Table 3, if male 2 entered a sexual relationship with a female whose previous male partner was positive for HPV type *x*, the odds of male 2 testing positive for that type increased 4.2-fold, CI:2.5-7.0. However, after adjusting for instances of female positivity up to male 2 enrolment, the OR was attenuated (1.4, CI:0.7-2.6).

The following covariates lowered the odds that male 2 would test positive for the same HPV type as male 1: time gaps between male 1 and 2 sampling ≥10.2 months (2.9, CI:1.3-6.2), <40.7 instances of vaginal sex in the downstream partnership (2.5, CI:1.1-5.7), and condom use >75% of the time in the downstream partnership (3.8, CI:1.7-8.7). The odds of male 2 positivity were not strongly impacted by his concurrent sex partner count (4.3, CI:2.6-7.2). Concerning individual subgenera, the relationship between HPV detection in males 1 and 2 was often unique for subgenus 3 compared to subgenera 1 and 2. While O/E ratios for subgenera 1 and 2 were similar to the overall estimate, that of subgenus 3 was larger (3.8, CI:1.7-7.0). The OR for male 2 testing positive for the same type as male 1 was also larger for subgenus 3 (9.9, CI:2.8-35.4), while subgenera 1 and 2 ORs were similar to the overall estimate. Additionally, for subgenus 3, the OR was higher when the time gap between male 1 and 2 sampling was ≥ 10.2 months, and when the downstream partnership was using condoms ≤ 75% of the time. Both covariates had the opposite influence on the OR estimate for subgenera 1 and 2.

Adjusting for the total number of genital samples provided by males 1 and 2 (i.e., male detection opportunities) did not change the overall OR. The number of days since the downstream partnerships' most recent vaginal sex encounter had a minimal impact on the OR (4.3, CI:2.6-7.1). However, when treated as a binary variable, the OR differed between downstream partnerships who had vaginal sex ≤ 3 days ago (6.0, CI:3.3-11.0) vs. > 3 days ago (1.3, CI:0.4-4.6).

4.2.5 Discussion

In this study of sequential young-adult heterosexual relationships, we found evidence of HPV infections originating in upstream relationships being transmitted to downstream partners via a linking partner (male 1↔female→male 2). Detection of the same HPV type in males 1 and 2 was observed 2.6 times more often than chance, indicating that HPV positivity in a female's sequential sex partners is not independent. The 4.2-fold higher odds that male 2 would test positive for an HPV type detected in male 1 were attenuated by the female partner's positivity for the same type, suggesting mediation via the linking female partner. When we adjusted for the number of female detections, each additional instance of type-specific HPV detection in the female partner increased the odds of male 2 positivity 2.2-fold, CI:1.8-2.7, on average. Hence, infection persistence in the linking female appears to be relevant to whether a particular HPV type becomes detectable in the downstream male.

To our knowledge, this is the first couple-based analysis of HPV transmission across sequential heterosexual relationships. Notwithstanding, our results are unsurprising in the context of couple-based analyses of current sex partnerships. Type-specific HPV concordance between partners is consistently higher than expected [4-6, 8, 10, 11]. A current partner's positivity is also a strong determinant for an uninfected partner's development of an incident infection via type-specific HPV transmission [7-12]. Gaps ≥ 10.2 months between testing males 1 and 2 for HPV

considerably lowered the odds of male 2 testing positive. This variable may be a crude proxy of the time elapsed between the downstream and upstream partnerships, which is a risk factor for STI diagnosis in downstream partners [24]. We recently estimated that genital infections persisted, on average, 10.3-14.8 months in HITCH study-enrolled women [22], which corroborates a role for female infection persistence in transmission to male 2. Presumably, infection clearance or latency in the linking partner before initiation of the downstream partnership decreases the odds of transmission to male 2.

Several sexual behaviours in the downstream partnership were relevant to the odds of male 2 testing positive for the same HPV type as male 1. We observed, in accordance with couple-based transmission studies, an increased risk of infection with increasing instances of vaginal sex [7, 10, 12] and decreasing frequency of condom use [7, 12]. Having concurrent male 2 partners had little impact on male 2 type-specific HPV concordance with male 1 infection. This is expected since male 2 infection via a concurrent partner is a function of the concurrent partner's infection status, which should be independent of male 1 type-specific HPV positivity.

Compared to subgenera 1 and 2, subgenus 3 HPV types had a large O/E ratio and crude OR. Our estimates of similar infection persistence across subgenera in the HITCH cohort cannot explain the higher odds of male 2 positivity observed with longer timelapses between testing male partners [22]. Subgenus 3 types also reversed the typically odds-lowering impacts of more-frequent condom use observed for subgenera 1 and 2. Their mucocutaneous tissue tropism may have allowed subgenus 3 HPV types to spread via sexual contact between tissue not covered by condoms (e.g., pubic hair follicles) [19].

The key strengths of our study and analysis are the enrolment of linked partnerships and longitudinal observation of the female partner. We acknowledge four important limitations.

Firstly, while partners were asked to refrain from sex 24 hours pre-sampling, we have estimated that 14.1% of detections in males and females in the HITCH study are attributable to deposition [25]. Recency of vaginal sex, considered on a continuous scale, minimally impacted the OR. However, we have detected Y chromosome DNA in female genital samples up to 3 days after vaginal sex in this cohort [23], and the odds of male 2 testing positive were insignificant when downstream partnerships' most-recent sex was ≤3 days ago. While we expect opposite-sex cells to dissipate faster from male genitalia during routine washing, cleaning the mucosal glans penis may be less common in uncircumcised males (60% of male 2) [26]. Secondly, combining male HPV DNA positivity into one measurement may have introduced misclassification. However, adjusting for the number of times the males were tested did not change OR estimates, suggesting that combining genital sample results did not strongly influence our estimates, despite differential detection opportunities. Thirdly, we ascertained sexual behaviour covariates via male 2 self-report. However, inter-partner reporting discrepancies were minimal for the upstream partnership, and we expect the same to hold true for the downstream partnership. Finally, the small number of linked partnerships and HPV types in our mixed effects models, as well as the low prevalence of the outcome (9%, overall) may have biased our fixed effects and variance-covariance estimates [27]. Future studies would benefit from larger numbers of linked partnerships and the assessment of both male↔female→male and female↔male→female transmission directionalities.

Our findings may have implications for HPV-related cancer prevention strategies such as gender-neutral vaccination. Unvaccinated females and males gain protection from HPV infection via herd effects when vaccinated individuals do not contract, and subsequently do not transmit, the virus [3]. According to our findings, had male 2 not entered a partnership with a female whose previous partner tested positive (and who was not persistently positive for that HPV type), the odds

that male 2 would test positive for the same infection would diminish. Vaccinating males may therefore prevent infection in current unvaccinated sex partners ("direct" herd effects) *and* downstream unvaccinated sexual connections ("indirect" herd effects). While vaccinating females alone probably also has "indirect" herd effects, males tend to have greater numbers of sex partners compared to females [28], and herd effects are augmented when vaccine coverage is high in groups that are more sexually active.

Our results provide evidence that HPV is transmissible in a chain of sequential heterosexual young adult partnerships. Positivity in an upstream partnership is a strong predictor of type-specific HPV positivity in a downstream male partner when the linking female partner is persistently positive for that type. These estimates suggest that vaccinating upstream male partners may exert "indirect" herd effects on downstream sexual connections.

4.2.6 Notes

Disclaimer. The funders played no role in study design, data collection/analysis, preparation of the manuscript, or the decision to submit it for publication.

Ethics approval. HITCH complies with all national/international regulations regarding research with human data and materials, including the Declaration of Helsinki. The study was conducted per the principles and articles stipulated by the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. Ethical approval was obtained from the institutional review boards at McGill University, Concordia University, and the Centre Hospitalier de l'Université de Montréal. Ethics renewal approval is requested annually from McGill University (study number A09-M77-04A). All subjects provided written informed consent for study participation.

4.2.7 Transparency Declaration

Conflicts of interest. A.W.A. received a graduate stipend from the Gerald Bronfman Department of Oncology, McGill University and a presenter's award from the Experimental Medicine Graduate Students' Society, McGill University. M.Z. and E.L.F. hold a patent related to the discovery "DNA methylation markers for early detection of cervical cancer," registered at the Office of Innovation and Partnerships, McGill University, Montréal, Québec, Canada (October 2018). F.C. reports grants from Réseau FRQS-SIDA during the conduct of the study, and grants to his institution for HPV-related work from Merck Sharp and Dome, Roche Diagnostics and Becton Dickinson outside of the submitted work. All other authors report no potential conflicts.

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Access to data. HITCH participant consent forms specified that data would be published in aggregate form and that individual-level data would only be available to study investigators. To access individual-level data, please contact Eduardo Franco at eduardo.franco@mcgill.ca. The protocol for the HITCH cohort study has been published [13]. Analytical codes and data dictionary are available on the McGill University Dataverse [29].

Author contributions. Andrew W. Arthur: methodology (lead), validation (lead), formal analysis (lead), writing – original draft (lead), visualization (lead); Mariam El-Zein: methodology (equal), data curation (equal, HITCH), writing – review and editing (lead), supervision (equal); Ann N. Burchell: conceptualization (equal, HITCH), investigation (lead, HITCH), writing – review and editing (equal), supervision (supporting), project administration (lead, HITCH), funding acquisition (lead, HITCH); Pierre-Paul Tellier: investigation (equal, HITCH), resources (equal, HITCH), project administration (equal, HITCH), writing – review and editing (equal); Francois Coutlée: validation (lead, HITCH), investigation (equal, HITCH), resources (equal, HITCH), writing – review and editing (equal). Eduardo L. Franco: conceptualization (lead), methodology (equal, HITCH), writing – review and editing (equal), supervision (lead), project administration (equal, HITCH), funding acquisition (lead, HITCH).

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4.2.9 Tables & Figures

M2-Table 1. Self-reported baseline characteristics of linked partnerships in the HITCH study.

Variable	Male 1	Female	Male 2
Sociodemographic and lifestyle characteristics			
Age in years, median (range)	22 (19-34)	20 (18-24)	24 (20-35)
Ethnicity, n (%)			
English Canadian	18 (42.9)	17 (40.5)	14 (33.3)
French Canadian	7 (16.7)	10 (23.8)	11 (26.2)
Black Canadian	2 (4.8)	--	3 (7.1)
European	--	--	3 (7.1)
Latin American	2 (4.8)	3 (7.1)	2 (4.8)
Multiple/Mixed Ethnicities	6 (14.3)	3 (7.1)	2 (4.8)
American	--	--	2 (4.8)
Middle Eastern/North African	3 (7.1)	3 (7.1)	2 (4.8)
South Asian	--	3 (7.1)	--
Other/missing	4 (9.5)	3 (7.1)	3 (7.1)
Circumcised, n (%)	26 (61.9)	NA	16 (38.1)
HPV-vaccinated, n (%)[a]	0 (0.0)	1 (2.4)	1 (2.4)
Smoked 100+ cigarettes; lifetime, n (%)	21 (50.0)	20 (47.6)	27 (64.3)
Age at vaginal coitarche, median (range)	17 (13-23)	16 (13-20)	16 (13-21)
Lifetime vaginal sex partners, median (range)	8 (0-54)	6 (1-25)	14 (2-80)
Behaviour during relationship with study partner[b]			
Had vaginal sex, n (%)	40 (95.2)	41 (97.6)	41 (97.6)
Months since first sex, median (IQR)	3.6 (2.8-4.8)	3.4 (2.2-4.8)	3.5 (1.8-5.5)
Instances of sex, median (IQR)	57.3 (34.6-78.9)	56.0 (37.7-103.0)	40.7 (10.0-86.1)
Days since last sex, median (IQR)	3 (2-5)	3 (2-5)	2 (2-5)
Condom Use, n (%)			
Never (0%)	8 (19.1)	6 (14.3)	4 (9.5)
Rarely (1-25%)	12 (28.6)	11 (26.2)	12 (28.6)
Some of the time (26-75%)	2 (4.8)	5 (11.9)	6 (14.3)
Most of the time (76-99%)	10 (23.8)	10 (23.8)	8 (19.1)
Always (100%)	8 (19.1)	9 (21.4)	11 (26.2)
Had study-external sex partners, n (%)	5 (11.9)	8 (19.1)	8 (19.1)
Study-external sex partners, median (range)	0 (0-10)	0 (0-15)	0 (0-4)

Abbreviations: NA, not applicable; HPV, human papillomavirus; IQR, interquartile range.

-- Ethnicity categories with less than 2 participants were included in the "Other/missing" category to prevent participant identification.

[a] Vaccination data were collected after vaccine's licensing in 2006.

[b] Relates to vaginal sex specifically, except "study-external sex partners," in which non-vaginal sex partners are included.

M2-Table 2. Type-specific HPV concordance between male 1 and male 2, overall and by subgenus.[a]

Alphapapillomavirus	HPV Type	Positivity Male 1/Male 2				Expected Concordance	Observed/Expected Concordance (95% CI)
		-/-	-/+	+/-	+/+		
All subgenera	Any	1,283	109	91	29	10.95	2.6 (1.9-3.5)
Subgenus 1	6	29	6	5	2	1.33	1.5 (0.0-4.0)
	11	42	0	0	0	0	NCE
	40	37	3	2	0	0.14	0
	42	29	4	6	3	1.5	2.0 (0.0-4.2)
	44	39	2	1	0	0.05	0
	54	35	3	3	1	0.38	2.6 (0.0-10.5)
	Any	211	18	17	6	2.19	2.7 (1.0-4.2)
Subgenus 2	16	27	5	4	6	2.62	2.3 (1.3-4.0)
	18	36	4	2	0	0.19	0
	26	42	0	0	0	0	NCE
	31	36	4	2	0	0.19	0
	33	41	1	0	0	0	NCE
	34	42	0	0	0	0	NCE
	35	41	1	0	0	0	NCE
	39	32	4	5	1	0.71	1.4 (0.0-4.7)
	45	39	2	1	0	0.05	0
	51	22	10	8	2	2.86	0.7 (0.0-1.7)
	52	39	1	2	0	0.05	0
	53	26	8	6	2	1.9	1.1 (0.0-2.4)
	56	29	8	4	1	1.07	0.9 (0.0-3.4)
	58	38	1	2	1	0.14	7.0 (0.0-21.0)
	59	34	3	4	1	0.48	2.1 (0.0-8.4)
	66	34	3	4	1	0.48	2.1 (0.0-9.3)
	67	32	6	4	0	0.57	0
	68	40	1	1	0	0.02	0
	69	42	0	0	0	0	NCE
	70	39	2	1	0	0.05	0
	73	32	5	4	1	0.71	1.4 (0.0- 4.7)
	82	36	3	3	0	0.21	0
	Any	779	72	57	16	6.95	2.3 (1.4-3.3)
Subgenus 3	61	37	2	3	0	0.14	0
	62	34	6	2	0	0.29	0
	71	41	1	0	0	0	NCE
	72	42	0	0	0	0	NCE
	81	40	1	1	0	0.02	0
	83	41	1	0	0	0	NCE
	84	28	3	7	4	1.83	2.2 (0.8-4.2)
	89	30	5	4	3	1.33	2.3 (0.0-5.0)
	Any	293	19	17	7	1.86	3.8 (1.7-7.0)

Abbreviations: HPV, human papillomavirus; CI, confidence interval; NCE, no concordance expected (inestimable).

[a] Subgenus 1 includes low oncogenic risk mucosal HPV types, subgenus 2 includes high oncogenic risk mucosal HPV types, and subgenus 3 includes commensal mucocutaneous HPV types [18, 19].

M2-Table 3. Crude, adjusted, and stratified odds ratios (95% confidence intervals) for the association of type-specific HPV positivity between male 1 and 2, overall and by subgenus.[a]

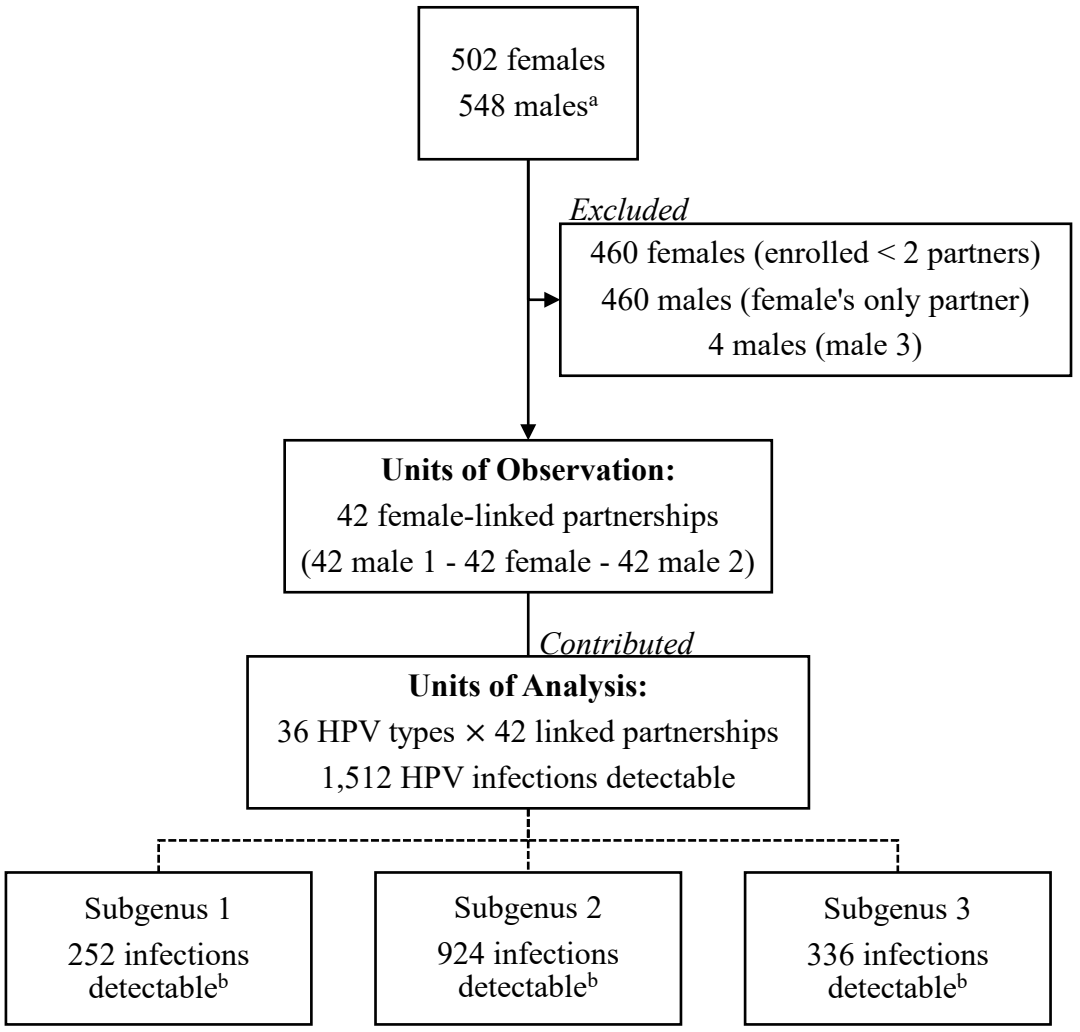
Type of Analysis	Covariate Stratum	Overall	Subgenus 1	Subgenus 2	Subgenus 3
Crude	--	4.2 (2.5-7.0)	4.3 (1.3-14.4)	3.4 (1.8-6.4)	9.9 (2.8-35.4)
HPV Positivity-Related Covariates					
Adjusted for instances of female positivity	--	1.4 (0.7-2.6)	0.2 (0.0-2.0)	1.6 (0.7-3.3)	1.0 (0.2-5.7)
Stratified by time between male 1 last available, and male 2 baseline samples	<10.2 months	5.8 (2.9-11.7)	7.5 (1.0-54.0)	5.7 (2.4-13.6)	6.6 (1.0-41.4)
	≥10.2 months	2.9 (1.3-6.2)	3.1 (0.6-15.8)	1.7 (0.6-4.9)	13.3 (2.3-76.7)
Sexual Behaviour-Related Covariates					
Adjusted for number of male 2 concurrent partners	--	4.3 (2.6-7.2)	4.5 (1.3-15.5)	3.5 (1.8-6.6)	10.2 (2.8-37.0)
Stratified by instances of sex[b]	< 40.7 instances	2.5 (1.1-5.7)	NC	2.3 (0.9-6.3)	5.3 (1.1-26.5)
	≥ 40.7 instances	6.4 (3.2-12.8)	11.3 (1.7-73.2)	4.7 (2.0-11.4)	29.6 (2.9-297.7)
Stratified by frequency of condom use[b]	≤ 75% of the time	4.6 (2.4-8.8)	4.5 (1.1-18.4)	6.1 (2.6-14.2)	2.2 (0.4-13.9)
	> 75% of the time	3.8 (1.7-8.7)	2.7 (0.2-29.8)	1.5 (0.5-4.6)	55.7 (5.9-527.1)
Additional Analyses					
Adjusted for sum of male 1 & 2 samples (detection opportunity)	--	4.2 (2.5-7.0)	4.6 (1.4-15.4)	3.3 (1.7-6.4)	9.7 (2.7-34.7)
Adjusted for recency of sex, continuous (female deposition)[b]	--	4.3 (2.6-7.1)	4.4 (1.3-14.9)	3.4 (1.8-6.6)	10.8 (2.9-40.1)
Stratified by recency of sex, binary (female deposition)[b]	≤ 3 days prior	6.0 (3.3-11.0)	5.2 (1.4-20.2)	4.4 (2.1-9.5)	17.0 (3.6-81.2)
	> 3 days prior	1.3 (0.4-4.6)	NC	1.7 (0.5-6.6)	NC

Abbreviations: HPV, human papillomavirus; NC, no concordance.

-- indicates not applicable

[a] Subgenus 1 includes low oncogenic risk mucosal HPVs 6, 11, 40, 42, 44, and 54; subgenus 2 includes high oncogenic risk mucosal HPVs 16, 18, 26, 31, 33, 34, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73 and 82; and subgenus 3 includes commensal mucocutaneous HPVs 61, 62, 71, 72, 81, 83, 84 and 89 [18, 19].

[b] Relates to vaginal sex in the upstream partnership, as reported by male 2 at baseline. 1 linked partnership was excluded (no vaginal sex). 1 additional linked partnership excluded from analyses stratified by instances of vaginal sex (missing data).



M2-Figure 1. Sample selection in the HITCH study and analytic framework.

M2-Figure 1 Legend:

⟶ Indicates changes in observational sample size.

——— Indicates data transformation from observational to analysis sample.

- - - - Indicates breakdown of analysis sample into Alphapapillomavirus subgenera.

[a] HITCH enrolled 548 couples. 42 women enrolled subsequent male partner(s) at follow-up.

[b] Subgenus 1 includes low oncogenic risk mucosal HPVs 6, 11, 40, 42, 44, and 54; subgenus 2 includes high oncogenic risk mucosal HPVs 16, 18, 26, 31, 33, 34, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73 and 82; and subgenus 3 includes commensal mucocutaneous HPVs 61, 62, 71, 72, 81, 83, 84 and 89 [18, 19].

CHAPTER 5. DISCUSSION

5.1 KEY FINDINGS

This thesis provided evidence to inform primary and secondary HPV-related cancer prevention by detailing HPV infection transmission, incidence and clearance in young heterosexual couples.

In Manuscript 1, we provided an extensive account of HPV type-specific infection natural history. We estimated an HPV incidence rate higher than estimates for women of a similar age,[33] which may be partially attributable to testing women for many HPV types, and partially attributable to HITCH-enrolled women's recent initation of a new sexual relationship.[9,34] Additionally, compared to meta-analyzed estimates, we observed more than double the average infection persistence.[39] While one could hypothesize that longer infection durations were a result of repeated reinfections from ongoing sex partners, there were indications that participants frequenty attended follow-up late; interval censoring may therefore be partially to blame. The persistence of HPV infections present at baseline was difficult to compare to that of incident infections due to differential right-censoring.

Notably, at the woman level, high oncogenic risk subgenus 2 infections present at baseline appeared to persist, on average 12.2 and 9.5 months longer than low-oncogenic risk subgenera 1 and 3 infections, respectively. This finding is consistent with a number of studies conducted at the woman-level, which have estimated a longer duration for high oncogenic risk HPV types compared to low oncogenic risk types, which suggests comparability between our study and others.[10,11,36,37,67] However, at the HPV-level, this pattern did not carry through. Comparing subgenus 2 infections to subgenera 1 and 3 infections, we found respective differences in median persistence of only 1.5 and 1.7 months (among infections present at baseline) and -0.4 and 0.5

months (among incident infections). These small differences do not suggest that oncogenic subgenus 2 infections persist longer than subgenera 1 and 3 infections.

A potential explanation for differences between findings at the woman- and HPV-levels relates to woman-level analyses' limited ability to account for the clearance of individual infections. Woman-level clearance events require infections of all HPV types within a subgenera to become undetectable, whereas HPV-level clearance events only require infections of one HPV type to become undetectable. Given clinical interest in oncogenic papillomaviruses, studies of HPV natural history have frequently tested participants for more high oncogenic risk HPV types than low oncogenic risk types. It is possible that the longer persistence of high oncogenic risk HPV infections is a methodological artefact created by assigning a probabilistically less-likely event to high oncogenic risk type groupings, and a probablistically more-likely event to low oncogenic risk type groupings. Future studies may benefit from investigating infection natural history with infections as the unit of analysis to prevent interpretive ambiguities that can arise from composite woman-level event definitions.

In Manuscript 2, we investigated transmission of HPV infections from upstream sexual partnerships (male 1↔female) to downstream sex partners (→male 2). In male 2, we observed HPV types detected in male 1 2.6 times more often than we would expect if the HPV positivity statuses of males 1 and 2 were independent. This is strong evidence against our null hypothesis (i.e., that male 1↔female→male 2 transmission did not occur).

The odds that male 2 would test positive for a given HPV type increased 4.2 times if he became the next sex partner of a female whose previous male partner was positive for that type. However, these odds were nullified after adjusting for the number of times the linking female

partner tested positive for the same HPV type (as of male 2 baseline). The attenuating impact of the number of instances of female positivity on the crude odds ratio is demonstrated in T-Table 5.

T-Table 5. Odds ratios (95% confidence intervals) for the association of type-specific HPV positivity between males 1 and 2, overall and by subgenera.[a]

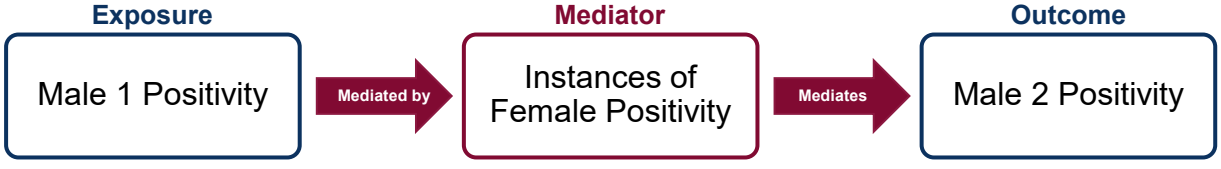
Model	Covariate	Overall	Subgenus 1	Subgenus 2	Subgenus 3
Crude	Male 1 Positivity[b]	4.2 (2.5-7.0)	4.3 (1.3-14.4)	3.4 (1.8-6.4)	9.9 (2.8-35.4)
Adjusted	Male 1 Positivity[b]	1.4 (0.7-2.6)	0.2 (0.0-2.0)	1.6 (0.7-3.3)	1.0 (0.2-5.7)
	Female Positivity[c]	2.2 (1.8-2.7)	10.7 (3.2-35.8)	1.7 (1.4-2.2)	4.4 (2.3-8.2)

[a] Subgenus 1 includes low oncogenic risk mucosal HPVs 6, 11, 40, 42, 44, and 54; subgenus 2 includes high oncogenic risk mucosal HPVs 16, 18, 26, 31, 33, 34, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73 and 82; and subgenus 3 includes commensal mucocutaneous HPVs 61, 62, 71, 72, 81, 83, 84 and 89 [13,44]

[b] Binary covariate (- or +).

[c] Continuous covariate (number of instances of positivity).

Further, in the adjusted regression model, the female positivity covariate's effect on the odds of male 2 positivity is powerful: each time the linking female partner tests positive for the same HPV type as male 1, the odds that male 2 will test positive for that type roughly double. The loss of the statistically significant association between male 1 and male 2 positivity when instances of female positivity are added to the model suggests the association may be mediated by persistent infection in the linking female partner (visualized in T-Figure 2).



T-Figure 2. Potential mediation of the association between male 1 and male 2 HPV positivity via persistent infection in the linking female partner.

Our results imply that if a female's previous (male 1) partner were not HPV positive, and she did not remain persistently positive for the same HPV type, the odds that male 2 would test positive for the type in question would not be different than chance. Therefore, vaccinating males against HPV might prevent incident infections in sequential sexual connections.

Several additional factors were associated with lower odds of male 2 testing positive for the same HPV type as male 1, most of which were logically consistent with findings from other couple-based HPV or STI studies. With respect to the female-male 2 sexual partnership, these factors included fewer instances of vaginal sex[27,30,65] and more frequent condom use.[27,65]

Assuming that in many cases, type-specific HPV concordance between males 1 and 2 was a result of transmission, the odds of subgenus 3 infections transmitting from upstream sexual partnerships to downstream sex partners were higher than those for subgenera 1 and 2 infections. Given subgenus 3 HPV types' negligible oncogenic risk,[13] this is not a matter of public health concern. However, the odds for transmission of subgenus 3 types were not lowered by more frequent condom use (as they were for subgenera 1 and 2 types). One hypothesis to explain increased inter-partnership subgenus 3 infection transmission pertains to subgenus 3 HPV types' tropism for mucocutaneous tissue. Cutaneotropic HPV virions are thought to preferentially infect stem cells in the rete pegs, dermal papillae and sweat apparatuses of the epithelium, and the bulge regions of the hair follicles.[13] Considering that condoms are designed to prevent contact between male and female genital tissues, but do not cover the cutaneous pubic region, perhaps transmission of subgenus 3 infections can occur via contact between the male and female pubic regions during intercourse.

5.2 Strengths and Limitations

The key strength of manuscripts 1 and 2 is the design of the HITCH study. Without extensive longitudinal couple-based data, it would not have been possible to analyze the natural history and etiology of HPV infection in such detail.

However, there are two noteworthy limitations applicable to both manuscripts. First, deposition of HPV DNA from recent sex between partners is probable. Measurement error of this sort is a well-documented phenomenon in couple-based HPV studies.[28] Based on the presence of Y chromosome DNA in female genital samples, we have previously estimated that about 14% of HPV DNA detections in males and females in the HITCH study were false positives caused by deposition from recent vaginal sex.[68] Y chromosome DNA appears to become undetectable in female vaginal samples about 3 days after vaginal intercourse.[69] However, participants were only instructed to refrain from vaginal sex for 24 hours before providing genital samples, and in most cases, 50% or more couples' most recent vaginal sex encounter was ≤3 days prior. Second, latent infection reactivation may have caused overestimation of new infections (i.e., estimates of incidence and transmission), while newly latent HPV infections may have caused underestimation of prevalent and incident infections (i.e., estimates of prevalence, incidence, and transmission) as well as underestimation of infection duration.

In Manuscript 1, the most important limitation was interval censoring, which may have overestimated the time required for infections to clear, and may have caused some incident infections and infection clearances to go unobserved in our data. In Manuscript 2, the most important limitation was the small number of linked partnerships and low prevalence of the outcome variable. One simulation study suggests this may have led to a biased estimate of the fixed effects and variance-covariance components of our mixed effects models.[70]

5.3 CONCLUSIONS

Altogether, this thesis has capitalized on the unique design of the HITCH Cohort Study to provide evidence for secondary and primary HPV-related cancer prevention. Firstly, HPV-level analyses did not evidentiate greater persistence of high oncogenic risk subgenus 2 types compared to low oncogenic risk subgenera 1 and 3 types. By using the infection as the unit of analysis, future cohort studies may produce more biologically-informed estimates of HPV infection natural history. Secondly, we found evidence of HPV transmission from upstream sexual partnerships to downstream male sex partners via linking female partners. Vaccinating males may therefore exert herd effects on unvaccinated downstream sexual connections.

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APPENDICES

M1-Table S1. Double detection of incident infection for individual HPV types, grouped types at the woman-level, and grouped types at the HPV-level, by subgenus.

	n[a]	Cumulative Detection of Infection, % (95% CI)			Detection Rate[b] (95% CI)	Time (months) to Detection (95% CI)			
		6 Months	12 Months	24 Months		Actuarial Mean[c]	Actuarial Median[c]	Conditional Mean[d]	Conditional Median[d]
Subgenus 1									
HPV6	435	0.2 (0.0, 1.7)	2.0 (1.0, 3.9)	5.2 (3.4, 8.1)	2.0 (1.3, 3.0)	47.4 (46.5, 48.2)	NR	15.2 (12.2, 18.1)	15.3 (10.6, 18.1)
HPV11[e]	451	0.0	0.0	0.0	0.0	--	NR	--	--
HPV40	442	0.0[f]	0.7 (0.2, 2.3)	2.0 (0.9, 4.1)	0.6 (0.3, 1.3)	48.8 (48.3, 49.3)	NR	14.3 (9.7, 18.9)	13.1 (6.7, 22.9)
HPV42	419	1.7 (0.8, 3.5)	4.0 (2.5, 6.5)	5.9 (3.9, 8.9)	2.3 (1.5, 3.4)	47.0 (46.1, 48.0)	NR	10.8 (7.9, 13.7)	9.4 (5.4, 11.7)
HPV44	445	0.2 (0.0, 1.6)	0.5 (0.1, 1.9)	0.7 (0.2, 2.3)	0.3 (0.1, 0.8)	49.1 (48.8, 49.5)	NR	9.0 (3.8, 14.3)	7.6 (4.2, NR)[g]
HPV54	426	0.0[f]	0.8 (0.3, 2.3)	3.2 (1.8, 5.7)	1.3 (0.8, 2.3)	48.0 (47.2, 48.7)	NR	18.4 (14.8, 22.0)	18.2 (9.4, 19.7)
Any Woman-Level	367	1.7 (0.8, 3.7)	6.4 (4.2, 9.5)	13.4 (10.0, 17.7)	5.9 (4.5, 7.8)	43.3 (41.8, 44.9)	NR	15.0 (12.8, 17.2)	15.3 (9.7, 18.0)
Any HPV-Level[h]	2,618	0.3 (0.2, 0.7)	1.3 (0.9, 1.8)	2.8 (2.2, 3.7)	1.1 (0.8, 1.4)	48.3 (46.3, 48.5)	NR	14.0 (12.1, 15.9)	12.6 (9.7, 17.0)
Subgenus 2									
HPV16	374	1.6 (0.7, 3.6)	2.2 (1.1, 4.4)	3.9 (2.3, 6.7)	1.8 (1.1, 2.9)	47.4 (46.5, 48.4)	NR	15.1 (10.7, 19.6)	12.7 (4.8, 21.8)
HPV18	437	0.0[f]	0.8 (0.2, 2.3)	1.4 (0.6, 3.3)	0.6 (0.3, 1.2)	48.8 (48.3, 49.3)	NR	15.8 (9.1, 22.5)	11.4 (8.4, NR)[g]
HPV26[e]	453	0.0	0.0	0.0	0.0	--	NR	--	--
HPV31	430	0.5 (0.1, 1.9)	1.3 (0.5, 3.0)	2.4 (1.3, 4.6)	1.0 (0.6, 1.9)	48.3 (47.7, 49.0)	NR	14.5 (10.1, 19.0)	13.0 (5.1, 19.7)
HPV33[e]	448	0.0	0.0	0.0	0.0	--	NR	--	--
HPV34[e]	450	0.0	0.0	0.0	0.0	--	NR	--	--
HPV35	450	0.2 (0.0, 1.6)	0.5 (0.1, 1.9)	0.7 (0.2, 2.2)	0.3 (0.1, 0.8)	49.2 (48.8, 49.5)	NR	8.4 (5.0, 11.8)	8.5 (4.6, NR)[g]
HPV39	421	0.5 (0.1, 1.9)	1.0 (0.4, 2.6)	3.7 (2.1, 6.2)	1.4 (0.8, 2.3)	48.0 (47.3, 48.8)	NR	13.7 (10.5, 16.8)	12.6 (7.1, 17.2)
HPV45	445	0.0[f]	0.0[f]	0.8 (0.3, 2.5)	0.3 (0.1, 0.8)	49.2 (48.8, 49.5)	NR	14.7 (12.8, 16.7)	14.6 (12.7, NR)[g]
HPV51	405	0.3 (0.0, 1.8)	1.9 (0.9, 3.9)	3.4 (1.9, 5.9)	1.5 (0.9, 2.5)	47.9 (47.1, 48.6)	NR	14.9 (11.2, 18.5)	12.2 (9.3, 18.6)
HPV52	418	0.7 (0.2, 2.2)	2.0 (1.0, 4.0)	2.6 (1.4, 4.8)	1.1 (0.6, 1.9)	48.3 (47.6, 49.0)	NR	10.7 (7.1, 14.3)	9.5 (4.1, 14.0)
HPV53	419	0.5 (0.1, 1.9)	2.6 (1.4, 4.7)	4.3 (2.7, 7.0)	1.8 (1.1, 2.8)	47.6 (46.7, 48.4)	NR	12.7 (9.6, 15.7)	10.6 (8.5, 13.1)
HPV56	432	0.0[f]	1.3 (0.5, 3.0)	3.1 (1.7, 5.5)	1.0 (0.6, 1.9)	48.4 (47.7, 49.0)	NR	13.6 (10.7, 16.5)	13.5 (9.4, 16.3)
HPV58	431	0.2 (0.0, 1.7)	1.5 (0.7, 3.3)	2.4 (1.3, 4.6)	1.0 (0.6, 1.9)	48.3 (47.6, 49.0)	NR	14.7 (9.8, 19.7)	11.7 (7.1, 22.8)
HPV59	426	0.5 (0.1, 1.9)	0.5 (0.1, 1.9)	2.2 (1.1, 4.4)	0.9 (0.5, 1.8)	48.3 (47.6, 49.0)	NR	16.9 (11.6, 22.1)	15.6 (4.8, 21.0)
HPV66	426	1.2 (0.5, 2.8)	2.2 (1.2, 4.2)	4.7 (2.9, 7.4)	1.7 (1.1, 2.7)	47.6 (46.8, 48.4)	NR	12.7 (9.2, 16.1)	11.9 (5.5, 16.9)
HPV67	427	0.5 (0.1, 1.9)	1.3 (0.5, 3.0)	3.0 (1.7, 5.3)	1.1 (0.6, 2.0)	48.2 (47.5, 48.9)	NR	13.4 (9.6, 17.3)	13.1 (5.3, 17.5)
HPV68	440	0.0[f]	0.7 (0.2, 2.2)	1.0 (0.4, 2.7)	0.5 (0.2, 1.1)	48.9 (48.5, 49.4)	NR	13.2 (6.2, 20.1)	7.4 (6.6, NR)[g]
HPV69[e]	453	0.0	0.0	0.0	0.0	--	NR	--	--
HPV70	450	0.0[f]	0.2 (0.0, 1.7)	0.5 (0.1, 2.0)	0.2 (0.0, 0.7)	49.3 (49.0, 49.5)	NR	10.6 (6.4, 14.8)	7.6 (7.6, NR)[g]
HPV73	435	1.2 (0.5, 2.8)	1.7 (0.8, 3.5)	3.7 (2.2, 6.2)	1.4 (0.8, 2.3)	48.0 (47.2, 48.7)	NR	12.2 (8.9, 15.5)	12.3 (4.6, 15.5)
HPV82	441	0.2 (0.0, 1.6)	0.7 (0.2, 2.2)	1.0 (0.4, 2.7)	0.4 (0.1, 1.0)	49.1 (48.7, 49.4)	NR	10.8 (4.8, 16.8)	8.3 (4.5, NR)[g]
Any Woman-Level	233	3.9 (2.0, 7.3)	9.8 (6.6, 14.5)	21.2 (16.2, 27.5)	9.5 (7.2, 12.5)	40.2 (37.9, 42.4)	NR	14.0 (11.9, 16.1)	12.8 (10.6, 14.6)
Any HPV-Level[h]	9,511	0.4 (0.2, 0.5)	1.0 (0.7, 1.3)	2.0 (1.6, 2.5)	0.8 (0.6, 1.0)	48.6 (46.6, 48.7)	NR	13.6 (12.3, 14.8)	12.3 (11.4, 13.5)
Subgenus 3									
HPV61	443	0.9 (0.4, 2.5)	1.2 (0.5, 2.8)	2.7 (1.4, 4.9)	1.2 (0.7, 2.1)	48.1 (47.4, 48.8)	NR	15.7 (10.9, 20.4)	15.1 (5.4, 22.0)
HPV62	416	0.7 (0.2, 2.3)	2.3 (1.2, 4.3)	4.1 (2.5, 6.8)	1.5 (0.9, 2.4)	47.9 (47.1, 48.7)	NR	11.0 (7.9, 14.0)	9.7 (5.1, 14.7)
HPV71[e]	451	0.0	0.0	0.0	0.0	--	NR	--	--
HPV72[e]	451	0.0	0.0	0.0	0.0	--	NR	--	--
HPV81	446	0.0[f]	0.2 (0.0, 1.7)	0.2 (0.0, 1.7)	0.1 (0.0, 0.6)	49.3 (49.2, 49.5)	NR	--	NR

HPV83	444	0.2 (0.0, 1.6)	0.5 (0.1, 1.9)	0.5 (0.1, 1.9)	0.3 (0.1, 0.8)	49.1 (48.8, 49.5)	NR	11.7 (1.6, 21.9)	6.5 (4.3, NR)[g]
HPV84	413	1.5 (0.7, 3.3)	2.6 (1.4, 4.7)	4.1 (2.5, 6.7)	1.7 (1.0, 2.7)	47.6 (46.8, 48.5)	NR	12.3 (8.7, 15.9)	10.6 (5.1, 16.9)
HPV89	405	1.8 (0.8, 3.7)	3.7 (2.2, 6.1)	6.8 (4.6, 9.9)	2.7 (1.9, 4.0)	46.5 (45.4, 47.6)	NR	13.2 (10.3, 16.1)	11.6 (6.9, 18.2)
Any Woman-Level	336	4.2 (2.5, 7.1)	8.0 (5.5, 11.6)	13.5 (10.1, 17.9)	5.8 (4.3, 7.7)	43.5 (41.9, 45.1)	NR	12.1 (9.9, 14.4)	10.1 (6.2, 13.1)
Any HPV-Level[h]	3,469	0.6 (0.4, 0.9)	1.2 (0.9, 1.6)	2.2 (1.7, 2.8)	0.9 (0.7, 1.1)	48.5 (46.5, 48.7)	NR	12.8 (10.8, 14.9)	11.4 (7.6, 14.7)
All 36 Types									
Any Woman-Level	192	3.7 (1.8, 7.5)	11.8 (8.0, 17.4)	30.4 (23.9, 38.1)	13.3 (10.2, 17.3)	37.2 (34.6, 39.9)	NR	14.1 (12.3, 15.9)	13.1 (12.0, 14.8)
Any HPV-Level[h]	15,598	0.4 (0.3, 0.5)	1.1 (0.9, 1.4)	2.2 (1.8, 2.6)	0.9 (0.7, 1.0)	48.5 (46.5, 48.7)	NR	13.5 (12.4, 14.5)	12.2 (10.6, 13.6)

Abbreviations: CI, confidence interval; HPV, human papillomavirus; NR, not reached.

-- indicates an insufficient number of women were at risk (i.e., 0) or experienced the outcome (i.e., 0 or 1) to estimate this value.

[a] Sample size does not apply to conditional mean/median; sample size for conditional statistics is the number of double detections.

[b] Rate per 1000 woman-months, excepting HPV-level analyses of grouped types, which are provided as rate per 1000 infection-months.

[c] Time to detection including women/types that were censored. Actuarial means were found to be unreliable estimates of average time to detection due to right-censoring.

[d] Time to detection conditional on event of interest (i.e., time to detection restricted to women/types that had a single detection during the study).

[e] HPV type was never detected among women included in this analysis.

[f] HPV type was not detected by this time point among women included in this analysis.

[g] One bound of the survival function's 95% CI never reached or fell below 50%.

[h] 95% CIs for cumulative detection estimates generated using bootstrap resampling of woman-clusters. 95% CIs for detection rate per 1000 infection-months estimated via woman-clustered jackknife. 95% CIs for actuarial and conditional mean time to detection determined by woman-cluster resampling bootstrap. 95% CIs for actuarial and conditional median time to detection affixed by the times at which each (woman-clustered bootstrap-based) 95% CI bound of the actuarial and conditional survival functions (respectively) reached or fell below 50%.

M1-Table S2. Conservative clearance of infection present at baseline for individual HPV types, grouped types at the woman-level, and grouped types at the HPV-level, by subgenus.

	n[a]	Percent of Infection Uncleared, % (95% CI)			Clearance	Time (months) to Clearance (95% CI)			
		6 Months	12 Months	24 Months	Rate[b] (95% CI)	Actuarial Mean[c]	Actuarial Median[c]	Conditional Mean[d]	Conditional Median[d]
Subgenus 1									
HPV6	18	69.8 (41.8, 86.3)	56.4 (29.4, 76.6)	49.4 (23.5, 70.9)	31.1 (15.6, 62.2)	19.9 (13.3, 26.6)	12.6 (5.7, NR)[e]	6.6 (4.0, 9.1)	5.7 (1.4, 11.3)
HPV11	2	NR	NR	NR	228.9 (57.2, 915.0)	4.4 (2.2, 6.5)	2.8 (2.8, NR)[e]	4.4 (2.2, 6.5)	2.8 (2.8, NR)[e]
HPV40	11	80.8 (42.4, 94.9)	57.7 (22.1, 81.9)	19.2 (1.0, 55.4)	52.5 (23.6, 116.9)	14.0 (8.7, 19.2)	12.6 (5.1, NR)[e]	9.9 (5.3, 14.5)	7.8 (4.7, NR)[e]
HPV42	34	84.9 (67.4, 93.4)	50.6 (31.6, 66.9)	24.3 (9.7, 42.4)	50.9 (33.2, 78.1)	16.0 (11.8, 20.1)	12.2 (8.0, 19.7)	9.5 (7.7, 11.4)	8.0 (7.1, 11.7)
HPV44	8	60.0 (19.6, 85.2)	60.0 (19.6, 85.2)	45.0 (10.8, 75.1)	33.4 (12.5, 89.0)	20.3 (9.6, 30.9)	13.5 (4.4, NR)[e]	7.1 (3.5, 10.8)	4.8 (4.4, NR)[e]
HPV54	27	88.9 (69.4, 96.3)	58.1 (37.0, 74.3)	28.4 (11.6, 48.0)	50.0 (31.9, 78.4)	16.8 (12.8, 20.7)	12.5 (8.8, 22.4)	12.5 (9.3, 15.7)	10.6 (8.1, 13.7)
All Woman-Level	86	80.8 (70.5, 87.8)	62.5 (50.8, 72.1)	46.7 (34.6, 57.8)	33.3 (24.7, 45.0)	21.1 (18.0, 24.1)	20.0 (12.2, NR)[e]	10.0 (8.1, 12.0)	8.0 (5.8, 11.2)
Any HPV-Level[f]	100	79.2 (71.3, 86.4)	53.9 (40.9, 62.5)	31.0 (21.6, 42.1)	46.4 (36.5, 59.3)	17.5 (14.7, 20.0)	12.5 (10.6, 14.5)	9.8 (8.4, 11.2)	8.0 (7.4, 9.9)
Subgenus 2									
HPV16	79	92.1 (83.3, 96.4)	79.2 (67.9, 87.0)	50.9 (37.9, 62.5)	25.0 (17.9, 35.0)	24.0 (21.0, 26.9)	24.0 (18.1, NR)[e]	12.8 (10.8, 14.8)	13.6 (8.9, 15.6)
HPV18	16	68.8 (40.5, 85.6)	50.0 (24.5, 71.1)	23.4 (6.5, 46.4)	64.2 (37.3, 110.6)	13.5 (9.5, 17.5)	11.9 (5.2, 18.2)	10.7 (7.3, 14.2)	11.7 (5.1, 12.4)
HPV26	0	--	--	--	--	--	--	--	--
HPV31	23	90.9 (68.1, 97.6)	71.7 (47.6, 86.2)	34.2 (14.3, 55.4)	41.6 (24.7, 70.3)	18.1 (13.5, 22.7)	13.5 (9.0, 30.2)	12.1 (8.5, 15.8)	12.0 (6.2, 13.5)
HPV33	5	60.0 (12.6, 88.2)	NR	NR	89.4 (28.8, 277.3)	7.2 (4.7, 9.7)	7.6 (4.1, NR)[e]	5.3 (3.6, 7.1)	4.3 (4.1, NR)[e]
HPV34	3	100.0[g]	33.3 (0.9, 77.4)	NR	107.4 (34.6, 333.1)	9.3 (5.5, 13.1)	7.3 (6.7, NR)[e]	9.3 (5.5, 13.1)	7.3 (6.7, NR)[e]
HPV35	3	100.0[g]	66.7 (5.4, 94.5)	NR	43.1 (10.8, 172.5)	15.7 (8.1, 23.3)	20.4 (6.2, NR)[e]	13.3 (3.5, 23.2)	6.2 (6.2, NR)[e]
HPV39	32	83.2 (64.2, 92.6)	65.7 (45.5, 79.9)	22.5 (7.7, 41.9)	41.6 (26.5, 65.2)	19.4 (14.2, 24.7)	17.7 (9.4, 19.7)	11.9 (9.2, 14.6)	11.9 (6.0, 17.7)
HPV45	8	75.0 (31.5, 93.1)	45.0 (10.8, 75.1)	30.0 (4.4, 62.8)	52.4 (21.8, 125.8)	15.3 (7.5, 23.2)	9.9 (5.5, NR)[e]	8.4 (6.0, 10.8)	8.3 (5.5, NR)[e]
HPV51	48	86.7 (72.7, 93.8)	58.9 (42.2, 72.2)	26.1 (11.4, 43.5)	40.1 (27.1, 59.3)	18.8 (15.0, 22.7)	17.9 (11.6, 21.8)	11.2 (8.9, 13.5)	10.1 (6.1, 13.2)
HPV52	35	87.5 (70.0, 95.1)	66.0 (45.7, 80.1)	40.7 (20.6, 60.0)	32.8 (20.1, 53.6)	20.2 (15.9, 24.5)	20.7 (8.7, NR)[e]	11.9 (8.3, 15.5)	7.4 (5.1, 17.7)
HPV53	34	93.8 (77.5, 98.4)	64.4 (44.9, 78.5)	45.2 (26.4, 62.2)	30.3 (18.8, 48.7)	22.5 (17.9, 27.2)	20.4 (11.5, NR)[e]	12.7 (9.6, 15.8)	9.7 (7.8, 17.2)
HPV56	21	85.7 (62.0, 95.2)	59.2 (34.2, 77.4)	18.5 (3.4, 43.2)	45.6 (26.5, 78.5)	17.6 (11.5, 23.7)	16.2 (7.8, 21.8)	10.9 (7.5, 14.2)	8.1 (5.1, 16.2)
HPV58	22	90.4 (66.8, 97.5)	62.2 (36.4, 80.0)	23.3 (6.6, 45.9)	47.2 (27.4, 81.2)	16.4 (11.9, 20.8)	12.9 (8.7, 21.1)	11.2 (8.6, 13.8)	9.9 (6.5, 12.9)
HPV59	27	85.2 (65.2, 94.2)	47.4 (27.0, 65.4)	12.9 (3.3, 29.4)	65.0 (42.4, 99.7)	13.0 (10.4, 15.5)	11.0 (8.0, 16.2)	11.0 (8.9, 13.1)	10.3 (7.7, 14.7)
HPV66	27	73.7 (52.6, 86.5)	41.0 (22.0, 59.1)	14.0 (3.7, 31.2)	73.0 (47.6, 111.9)	11.6 (8.9, 14.3)	8.5 (7.5, 14.7)	9.0 (7.2, 10.8)	8.0 (4.8, 10.2)
HPV67	26	80.4 (59.2, 91.4)	51.7 (30.8, 69.1)	NR	68.3 (44.0, 105.8)	12.5 (9.9, 15.1)	12.0 (7.8, 17.7)	10.7 (8.2, 13.2)	8.0 (5.4, 14.5)
HPV68	13	100.0[g]	75.0 (40.8, 91.2)	50.0 (20.9, 73.6)	24.3 (10.9, 54.1)	22.8 (17.3, 28.2)	19.7 (9.8, NR)[e]	13.5 (10.4, 16.6)	11.7 (8.5, NR)[e]
HPV69	0	--	--	--	--	--	--	--	--
HPV70	3	100.0[g]	100.0[g]	50.0 (0.6, 91.0)	15.6 (2.2, 110.4)	24.7 (14.6, 34.9)	17.4 (17.4, NR)[e]	--	NR
HPV73	18	83.3 (56.8, 94.3)	43.3 (18.8, 65.7)	21.6 (5.4, 44.8)	51.2 (29.1, 90.2)	15.0 (10.4, 19.6)	12.0 (9.7, 18.4)	10.3 (7.7, 12.8)	9.9 (3.7, 12.6)
HPV82	12	55.0 (23.2, 78.3)	12.2 (0.7, 40.6)	NR	116.9 (62.9, 217.2)	8.0 (5.1, 10.8)	6.1 (4.1, 11.5)	7.4 (4.7, 10.1)	5.5 (2.8, 9.3)
All Woman-Level	220	94.8 (90.8, 97.1)	87.1 (81.6, 91.1)	64.2 (56.3, 71.0)	15.6 (12.2, 19.8)	31.1 (29.1, 33.2)	NR	14.2 (12.6, 15.9)	14.6 (12.0, 16.3)
Any HPV-Level[f]	455	85.6 (81.6, 88.8)	60.5 (55.8, 64.8)	30.1 (24.4, 34.5)	42.4 (37.8, 47.5)	20.0 (17.8, 21.4)	15.5 (13.5, 17.7)	11.1 (10.4, 11.9)	9.8 (8.5, 11.0)
Subgenus 3									
HPV61	10	77.8 (36.5, 93.9)	66.7 (28.2, 87.8)	53.3 (17.7, 79.6)	30.7 (12.8, 73.7)	21.0 (12.5, 29.4)	26.7 (3.9, NR)[e]	12.3 (5.0, 19.7)	9.7 (3.9, NR)[e]
HPV62	37	88.6 (72.4, 95.6)	67.7 (49.2, 80.7)	63.5 (44.3, 77.6)	22.2 (13.1, 37.4)	24.8 (20.3, 29.4)	NR	10.7 (6.8, 14.6)	7.4 (5.9, 8.8)
HPV71	2	100.0[g]	NR	NR	61.0 (8.6, 433.0)	--	9.9 (NR, NR)[e]	--	NR
HPV72[h]	2	100.0	100.0	100.0	0.0	--	NR	--	--
HPV81	7	100.0[g]	100.0[g]	NR	36.2 (11.7, 112.2)	15.0 (13.8, 16.1)	14.2 (13.5, NR)[e]	14.6 (13.3, 15.8)	14.2 (13.5, NR)[e]
HPV83	9	88.9 (43.3, 98.4)	77.8 (36.5, 93.9)	58.3 (15.7, 85.5)	21.0 (6.8, 65.0)	24.7 (14.6, 34.9)	NR	8.1 (4.4, 11.7)	6.1 (5.5, NR)[e]
HPV84	40	79.4 (63.0, 89.1)	39.0 (23.1, 54.6)	25.5 (12.0, 41.4)	62.3 (43.0, 90.2)	14.5 (10.5, 18.5)	8.5 (6.7, 13.1)	9.2 (6.9, 11.5)	7.3 (6.1, 8.5)

HPV89	48	87.2 (73.7, 94.0)	62.4 (46.0, 75.2)	39.2 (21.7, 56.3)	35.4 (23.3, 53.7)	22.3 (17.2, 27.4)	16.2 (9.7, NR)[e]	9.6 (7.7, 11.4)	8.8 (5.7, 11.3)
All Woman-Level	117	86.6 (78.7, 91.7)	71.7 (62.0, 79.3)	56.4 (45.4, 66.0)	24.0 (17.9, 32.1)	26.2 (23.1, 29.3)	NR	10.3 (8.5, 12.2)	8.5 (6.1, 10.4)
Any HPV-Level[f]	155	85.9 (78.8, 91.0)	60.2 (49.9, 67.4)	44.0 (33.7, 52.2)	35.5 (27.8, 45.4)	21.8 (18.0, 24.6)	16.2 (11.3, 25.0)	10.0 (8.7, 11.3)	8.2 (6.7, 8.8)
All 36 Types									
All Woman-Level	261	94.9 (91.3, 97.0)	88.4 (83.6, 91.8)	74.7 (68.2, 80.1)	11.8 (9.2, 15.1)	33.3 (31.5, 35.0)	NR	13.8 (11.9, 15.7)	13.1 (9.8, 16.1)
Any HPV-Level[f]	710	84.8 (80.7, 87.4)	59.5 (55.0, 63.3)	32.9 (28.4, 37.6)	41.4 (37.1, 46.2)	20.2 (18.3, 21.5)	15.3 (13.1, 16.6)	10.7 (10.1, 11.4)	8.9 (8.3, 9.9)

Abbreviations: CI, confidence interval; HPV, human papillomavirus; NR, not reached.

-- indicates an insufficient number of women were at risk (i.e., 0) or experienced the outcome (i.e., 0 or 1) to estimate this value.

[a] Sample size does not apply to conditional mean/median; sample size for conditional statistics is the number of conservative clearances.

[b] Rate per 1000 woman-months, excepting HPV-level analyses of grouped types, which are provided as rate per 1000 infection-months.

[c] Time to clearance including women/infections that were censored.

[d] Time to clearance conditional on event of interest (i.e., time to clearance restricted to women/infections that had a conservative clearance during the study).

[e] Bound(s) of the survival function's 95% CI never reached or fell below 50%.

[f] 95% CIs for uncleared infection estimates generated using bootstrap resampling of woman-clusters. 95% CIs for clearance rate per 1000 infection-months estimated via woman-clustered jackknife. 95% CIs for actuarial and conditional mean time to clearance determined by woman-cluster resampling bootstrap. 95% CIs for actuarial and conditional median time to clearance affixed by the times at which each (woman-clustered bootstrap-based) 95% CI bound of the actuarial and conditional survival functions (respectively) reached or fell below 50%.

[g] HPV type was not cleared by this time point among women included in this analysis.

[h] HPV type was never cleared among women included in this analysis.

M1-Table S3. Conservative clearance of incident infection for individual HPV types, grouped types at the woman-level, and grouped types at the HPV-level, by subgenus.

	n[a]	Percent of Infection Uncleared, % (95% CI)			Clearance	Time (months) to Clearance (95% CI)			
		6 Months	12 Months	24 Months	Rate[b] (95% CI)	Actuarial Mean[c]	Actuarial Median[c]	Conditional Mean[d]	Conditional Median[d]
Subgenus 1									
HPV6	32	83.0 (63.9, 92.6)	47.3 (25.0, 66.7)	20.3 (1.7, 53.4)	48.3 (28.6, 81.5)	14.3 (11.0, 17.7)	10.5 (8.5, NR)[e]	8.6 (6.3, 11.0)	7.6 (4.8, 9.6)
HPV11[f]	1	NR	NR	NR	0.0	--	NR	--	--
HPV40	14	92.3 (56.6, 98.9)	73.9 (38.5, 90.8)	NR	24.4 (9.1, 64.9)	16.7 (13.0, 20.3)	16.2 (8.7, NR)[e]	10.0 (6.1, 13.9)	8.7 (5.2, NR)[e]
HPV42	34	87.3 (69.6, 95.1)	67.7 (46.6, 81.9)	41.9 (19.4, 63.0)	32.1 (18.6, 55.3)	18.8 (14.8, 22.8)	16.0 (10.8, NR)[e]	9.9 (7.5, 12.2)	8.6 (5.6, 13.7)
HPV44	4	100.0[g]	66.7 (5.4, 94.5)	NR	24.7 (3.5, 175.7)	14.5 (8.6, 20.4)	NR	--	NR
HPV54	19	89.5 (64.1, 97.3)	78.3 (42.9, 93.2)	78.3 (42.9, 93.2)	14.5 (4.7, 45.0)	20.8 (16.8, 24.7)	NR	5.7 (1.9, 9.5)	3.7 (3.0, NR)[e]
All Woman-Level	69	88.1 (77.6, 93.9)	68.7 (53.9, 79.6)	41.4 (19.1, 62.6)	27.8 (18.3, 42.2)	19.6 (16.5, 22.7)	22.1 (14.7, NR)[e]	9.4 (7.4, 11.4)	8.7 (5.3, 10.8)
Any HPV-Level[h]	104	88.4 (81.3, 93.4)	72.7 (63.0, 79.9)	64.5 (53.6, 72.1)	18.3 (13.1, 25.9)	26.9 (23.5, 29.1)	NR	8.9 (7.6, 10.5)	NR
Subgenus 2									
HPV16	22	88.5 (61.4, 97.0)	77.5 (42.1, 92.8)	NR	26.1 (10.9, 62.7)	15.2 (11.9, 18.6)	15.3 (9.0, NR)[e]	9.5 (5.9, 13.1)	9.0 (4.8, NR)[e]
HPV18	10	88.9 (43.3, 98.4)	76.2 (33.2, 93.5)	76.2 (33.2, 93.5)	13.9 (3.5, 55.5)	24.6 (17.8, 31.4)	NR	6.7 (5.1, 8.3)	5.6 (5.6, NR)[e]
HPV26	0	--	--	--	--	--	--	--	--
HPV31	19	94.1 (65.0, 99.2)	70.6 (38.9, 88.0)	NR	28.2 (12.7, 62.7)	15.9 (13.2, 18.6)	19.7 (8.9, NR)[e]	11.6 (7.5, 15.6)	8.9 (5.3, NR)[e]
HPV33	4	50.0 (5.8, 84.5)	NR	NR	153.1 (57.5, 408.0)	6.5 (4.5, 8.5)	5.5 (3.7, NR)[e]	6.5 (4.5, 8.5)	5.5 (3.7, NR)[e]
HPV34[f]	2	100.0	NR	NR	0.0	--	NR	--	--
HPV35	4	100.0[g]	100.0[g]	NR	18.4 (2.6, 130.9)	20.5 (17.7, 23.3)	18.5 (18.5, NR)[e]	--	NR
HPV39	19	94.7 (68.1, 99.2)	67.6 (37.9, 85.4)	48.3 (19.5, 72.3)	30.6 (14.6, 64.2)	19.6 (14.0, 25.3)	14.7 (8.5, NR)[e]	9.1 (6.8, 11.5)	8.5 (4.7, 12.6)
HPV45	8	87.5 (38.7, 98.1)	87.5 (38.7, 98.1)	87.5 (38.7, 98.1)	10.5 (1.5, 74.5)	25.5 (20.1, 31.0)	NR	--	NR
HPV51	23	86.7 (64.3, 95.5)	70.1 (39.9, 87.2)	48.1 (17.7, 73.4)	27.2 (12.9, 57.0)	19.2 (14.3, 24.1)	16.3 (11.3, NR)[e]	9.2 (5.5, 12.9)	9.4 (3.6, 15.2)
HPV52	19	94.7 (68.1, 99.2)	53.3 (27.9, 73.3)	16.7 (1.3, 48.0)	50.0 (27.7, 90.3)	14.8 (10.8, 18.7)	13.7 (6.8, 23.0)	10.2 (7.0, 13.4)	9.0 (6.2, 13.7)
HPV53	25	87.5 (66.1, 95.8)	76.5 (51.8, 89.7)	68.8 (41.7, 85.2)	22.2 (10.0, 49.5)	19.2 (15.5, 22.9)	NR	6.5 (3.8, 9.1)	4.2 (3.6, NR)[e]
HPV56	16	85.7 (53.9, 96.2)	43.5 (14.0, 70.3)	NR	49.3 (23.5, 103.4)	11.8 (8.9, 14.7)	9.2 (7.9, NR)[e]	8.9 (6.2, 11.5)	8.2 (5.3, 9.2)
HPV58	13	100.0[g]	100.0[g]	66.7 (5.4, 94.5)	5.2 (0.7, 36.7)	30.4 (23.9, 36.9)	NR	--	NR
HPV59	18	82.2 (54.3, 93.9)	63.4 (31.1, 83.7)	63.4 (31.1, 83.7)	27.2 (11.3, 65.4)	21.8 (15.4, 28.2)	NR	6.0 (4.2, 7.9)	5.6 (3.4, NR)[e]
HPV66	35	81.7 (63.7, 91.3)	47.6 (25.7, 66.6)	NR	57.8 (35.9, 93.0)	11.9 (9.5, 14.4)	10.3 (8.6, 14.9)	8.7 (6.5, 10.9)	8.6 (4.6, 10.3)
HPV67	25	100.0[g]	56.5 (31.2, 75.5)	NR	41.1 (22.7, 74.2)	13.3 (11.2, 15.4)	14.7 (8.3, NR)[e]	10.2 (8.4, 12.0)	8.5 (7.4, 13.3)
HPV68	6	80.0 (20.4, 96.9)	53.3 (6.8, 86.3)	NR	38.5 (9.6, 153.9)	12.0 (8.5, 15.4)	NR	8.0 (4.6, 11.4)	5.6 (5.6, NR[e]
HPV69	0	--	--	--	--	--	--	--	--
HPV70[f]	5	100.0	100.0	100.0	0.0	--	NR	--	--
HPV73	21	95.0 (69.5, 99.3)	63.3 (35.7, 81.7)	NR	44.7 (24.1, 83.1)	14.2 (11.6, 16.8)	16.3 (8.8, 17.2)	11.4 (8.7, 14.1)	9.0 (4.8, 16.3)
HPV82	9	88.9 (43.3, 98.4)	31.8 (4.9, 64.7)	NR	58.0 (24.1, 139.3)	10.6 (7.8, 13.5)	9.4 (3.8, NR)[e]	8.0 (6.1, 9.8)	8.9 (3.8, NR)[e]
All Woman-Level	68	95.4 (86.5, 98.5)	78.6 (64.3, 87.7)	65.2 (44.2, 80.0)	16.3 (9.7, 27.5)	29.8 (25.3, 34.2)	NR	9.1 (6.5, 11.6)	8.1 (4.9, 10.1)
Any HPV-Level[h]	303	90.4 (86.3, 93.6)	72.1 (67.1, 77.3)	61.1 (54.6, 66.8)	20.5 (16.6, 25.6)	29.8 (24.6, 31.7)	NR	9.3 (8.4, 10.2)	NR
Subgenus 3									
HPV61	16	92.9 (59.1, 99.0)	83.6 (48.0, 95.7)	NR	17.9 (5.8, 55.4)	19.0 (14.5, 23.5)	NR	8.5 (5.1, 11.9)	7.9 (5.2, NR)[e]
HPV62	25	96.0 (74.8, 99.4)	78.8 (51.8, 91.7)	51.7 (22.1, 74.9)	27.2 (13.6, 54.4)	20.3 (15.4, 25.2)	29.0 (12.2, NR)[e]	12.4 (7.5, 17.3)	10.8 (3.7, 14.4)
HPV71	0	--	--	--	--	--	--	--	--
HPV72	0	--	--	--	--	--	--	--	--
HPV81	2	100.0[g]	100.0[g]	NR	44.8 (6.3, 318.2)	--	12.2 (NR, NR)[e]	--	NR
HPV83	7	100.0[g]	20.0 (0.8, 58.2)	NR	66.0 (24.8, 175.9)	9.6 (7.9, 11.3)	8.8 (7.3, NR)[e]	8.7 (7.7, 9.8)	8.5 (7.3, NR)[e]
HPV84	34	79.3 (59.4, 90.2)	52.6 (31.2, 70.2)	46.8 (25.4, 65.6)	39.0 (22.6, 67.1)	18.1 (13.4, 22.7)	13.9 (6.9, NR)[e]	6.9 (5.4, 8.4)	6.1 (4.5, 8.5)

HPV89	43	90.2 (75.9, 96.2)	69.5 (51.3, 82.0)	54.9 (29.0, 74.7)	25.7 (14.9, 44.3)	21.0 (17.3, 24.7)	NR	8.3 (5.9, 10.7)	6.7 (4.2, 10.5)
All Woman-Level	71	89.4 (79.1, 94.8)	70.6 (56.6, 80.7)	52.4 (35.2, 67.0)	29.2 (19.6, 43.6)	20.3 (17.3, 23.2)	29.0 (12.9, NR)[e]	9.4 (7.1, 11.7)	6.8 (5.7, 10.8)
Any HPV-Level[h]	127	90.5 (83.7, 94.5)	73.0 (64.3, 79.8)	65.2 (53.8, 72.4)	19.4 (14.1, 27.1)	26.6 (23.5, 28.9)	NR	8.8 (7.3, 10.5)	NR
All 36 Types									
All Woman-Level	65	96.8 (87.7, 99.2)	85.1 (72.3, 92.3)	72.1 (50.6, 85.5)	11.8 (6.5, 21.3)	31.9 (27.9, 36.0)	NR	9.7 (6.8, 12.7)	8.7 (5.3, 12.6)
Any HPV-Level[h]	534	90.0 (86.9, 92.4)	72.5 (68.4, 76.8)	62.7 (57.9, 66.9)	19.8 (16.8, 23.4)	30.1 (25.3, 31.4)	NR	9.1 (8.4, 9.9)	NR

Abbreviations: CI, confidence interval; HPV, human papillomavirus; NR, not reached.

-- indicates an insufficient number of women were at risk (i.e., 0) or experienced the outcome (i.e., 0 or 1) to estimate this value.

[a] Sample size does not apply to conditional mean/median; sample size for conditional statistics is the number of conservative clearances.

[b] Rate per 1000 woman-months, excepting HPV-level analyses of grouped types, which are provided as rate per 1000 infection-months.

[c] Time to clearance including women/infections that were censored.

[d] Time to clearance conditional on event of interest (i.e., time to clearance restricted to women/infections that had a conservative clearance during the study).

[e] Bound(s) of the survival function's 95% CI never reached or fell below 50%.

[f] HPV type was never cleared among women included in this analysis.

[g] HPV type was not cleared by this time point among women included in this analysis.

[h] 95% CIs for uncleared infection estimates generated using bootstrap resampling of woman-clusters. 95% CIs for clearance rate per 1000 infection-months estimated via woman-clustered jackknife. 95% CIs for actuarial and conditional mean time to clearance determined by woman-cluster resampling bootstrap. 95% CIs for actuarial and conditional median time to clearance affixed by the times at which each (woman-clustered bootstrap-based) 95% CI bound of the actuarial and conditional survival functions (respectively) reached or fell below 50%.

M1-Table S4. Sensitivity analysis: Actuarial mean time (months) to detection of incident infection with survival functions extended exponentially to 0 for individual HPV types, grouped types at the woman-level, and grouped types at the HPV-level, by subgenus.

	Single Detection		Double Detection	
	Mean (95% CI)	**Successful Reps. (%)**	**Mean (95% CI)**	**Successful Reps. (%)**
Subgenus 1				
HPV6	223.1 (117.5, 441.9)	100.0	742.1 (487.6, 1,240.4)	100.0
HPV11	1,844.4 (661.2, 17,133.2)	97.4	--	---
HPV40	256.2 (87.7, 958.7)	100.0	2,508.8 (1,336.9, 7,994.4)	100.0
HPV42	193.7 (122.3, 306.4)	100.0	723.5 (475.0, 1,206.4)	100.0
HPV44	914.2 (464.1, 2,932.4)	100.0	6,631.4 (2,814.9, 21,385.5)	95.5
HPV54	377.4 (244.7, 647.1)	100.0	926.4 (530.9, 1,961.8)	100.0
Any Woman-Level	101.8 (78.8, 130.7)	100.0	230.4 (171.5, 321.4)	100.0
Any HPV-Level[a]	348.9 (236.5, 514.0)	100.0	1,417.2 (1,078.0, 1,916.2)	100.0
Subgenus 2				
HPV16	290.8 (178.3, 522.6)	100.0	713.4 (427.4, 1,393.3)	100.0
HPV18	827.9 (477.0, 2,206.7)	100.0	2,254.4 (1,087.8, 9,565.9)	99.5
HPV26	18,369.3 (4,677.2, 19,061.6)	62.6	--	--
HPV31	276.1 (124.1, 704.0)	100.0	1,426.7 (834.5, 3,639.8)	100.0
HPV33	1,123.2 (388.3, 9,839.7)	99.7	--	--
HPV34	8,656.8 (3,300.0, 18,962.7)	87.0	--	--
HPV35	2,714.8 (1,203.0, 10,662.2)	99.8	6,815.1 (2,897.6, 21,583.3)	95.1
HPV39	394.6 (224.1, 762.2)	100.0	1,199.3 (748.5, 2,393.7)	100.0
HPV45	286.1 (97.0, 1,638.4)	100.0	6,055.3 (2,603.9, 18,814.3)	94.3
HPV51	194.3 (88.8, 453.3)	100.0	985.3 (606.7, 1,976.5)	100.0
HPV52	192.4 (78.8, 592.6)	100.0	1,620.6 (985.3, 3,669.8)	100.0
HPV53	370.7 (253.7, 560.2)	100.0	883.3 (573.9, 1,567.5)	100.0
HPV56	266.4 (99.5, 1,073.1)	100.0	1,598.5 (961.1, 3,491.8)	100.0
HPV58	843.1 (502.2, 1,695.8)	100.0	1,279.5 (723.0, 3,341.2)	100.0
HPV59	385.4 (187.0, 940.9)	100.0	1,164.2 (585.9, 3,202.9)	100.0
HPV66	158.3 (77.1, 368.3)	100.0	926.6 (608.8, 1,689.3)	100.0
HPV67	419.5 (263.5, 718.4)	100.0	1,302.8 (796.3, 2,736.0)	100.0
HPV68	2,739.6 (1,440.4, 10,049.3)	99.6	3,397.9 (1,647.4, 15,699.2)	98.9
HPV69	--	--	--	--
HPV70	2,209.5 (1,084.4, 8,069.4)	99.8	9,835.8 (3,851.2, 21,138.3)	84.7
HPV73	370.0 (178.9, 899.8)	100.0	1,188.1 (769.3, 2,254.4)	100.0
HPV82	1,791.4 (1,040.6, 4,279.5)	100.0	4,774.3 (2,205.4, 20,347.1)	98.2
Any Woman-Level	46.5 (30.7, 74.7)	100.0	148.0 (106.4, 211.9)	100.0
Any HPV-Level[a]	462.6 (305.6, 679.9)	100.0	1,892.1 (1,540.6, 2,339.2)	100.0
Subgenus 3				
HPV61	562.5 (366.5, 972.5)	100.0	1,160.4 (680.3, 2,448.7)	100.0
HPV62	129.6 (66.0, 459.9)	100.0	1,168.5 (753.2, 2,173.4)	100.0
HPV71	--	--	--	--
HPV72	--	--	--	--
HPV81	1,931.4 (888.5, 10,161.0)	99.6	20,643.8 (5,167.0, 21,187.7)	65.0
HPV83	2,608.7 (1,435.7, 9,580.1)	99.9	5,877.5 (2,391.1, 21,533.9)	93.9
HPV84	167.1 (90.7, 313.0)	100.0	918.7 (579.4, 1,639.4)	100.0
HPV89	229.1 (165.8, 325.9)	100.0	530.9 (351.7, 908.0)	100.0
Any Woman-Level	56.4 (37.6, 91.8)	100.0	261.2 (189.7, 359.7)	100.0
Any HPV-Level[a]	403.9 (281.2, 596.0)	100.0	1,715.7 (1,300.2, 2,258.2)	100.0
All 36 Types				
Any Woman-Level	45.8 (28.9, 71.9)	100.0	106.7 (77.3, 146.1)	100.0
Any HPV-Level[a]	426.0 (298.5, 591.6)	100.0	1,753.8 (1,457.7, 2,102.7)	100.0

Abbreviations: CI, confidence interval; HPV, human papillomavirus; reps., replications.

-- indicates an insufficient number of women were at risk (i.e., 0) or experienced the outcome (i.e., 0 or 1) to estimate this value.

[a] 95% CIs for mean times to detection determined by woman-cluster resampling bootstraps.

M1-Table S5. Sensitivity analysis: Actuarial mean time (months) to clearance of infection with survival functions extended exponentially to 0 for individual HPV types, grouped types at the woman-level, and grouped types at the HPV-level, by subgenus.

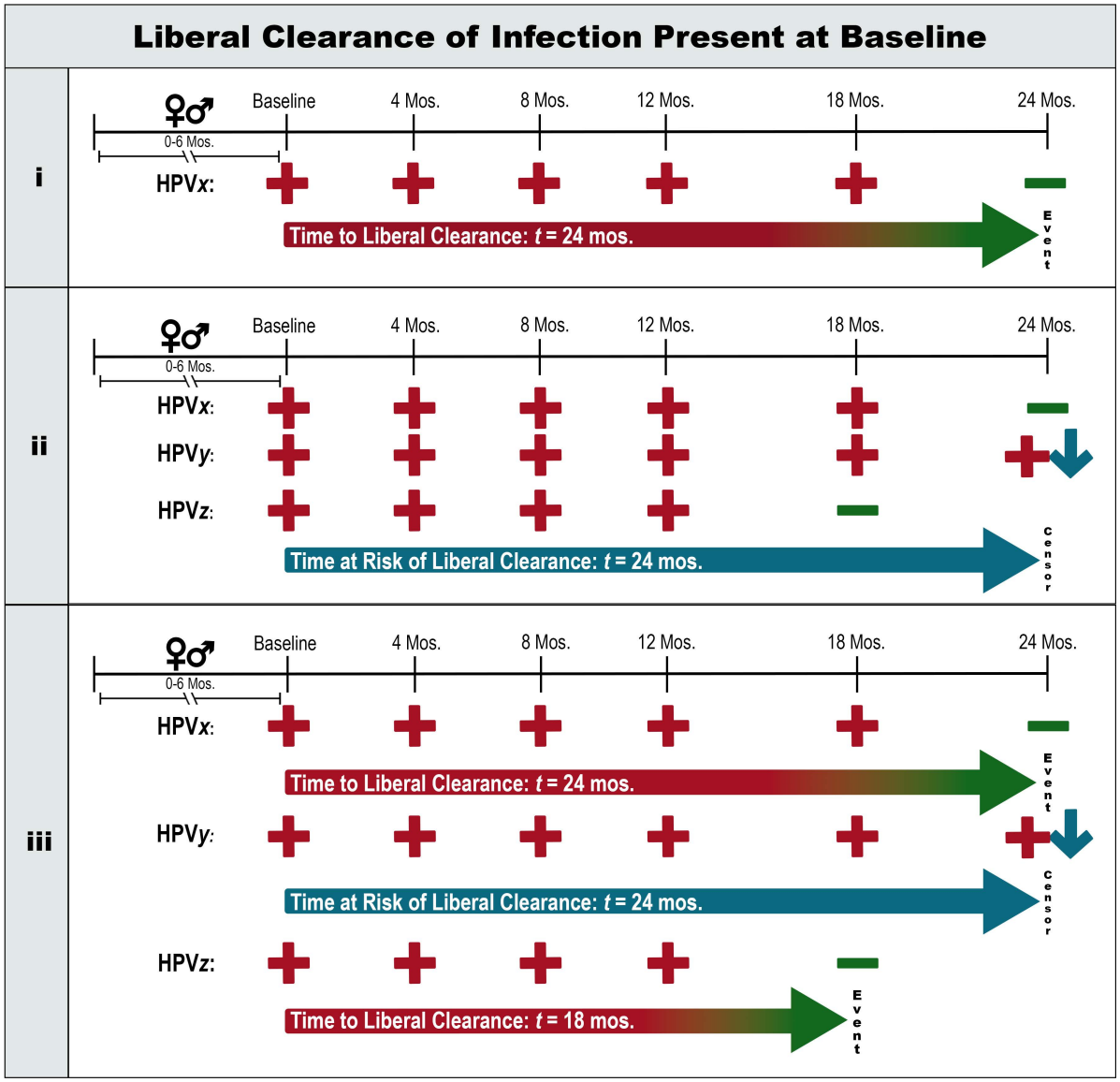
	Liberal Clearance				Conservative Clearance			
	Infections Present at Baseline		Incident Infections		Infections Present at Baseline		Incident Infections	
	Mean (95% CI)	Successful Reps. (%)	Mean (95% CI)	Successful Reps. (%)	Mean (95% CI)	Successful Reps. (%)	Mean (95% CI)	Successful Reps. (%)
Subgenus 1								
HPV6	13.7 (9.3, 29.9)	100.0	12.1 (9.1, 17.0)	100.0	43.3 (17.8, 107.5)	100.0	17.5 (11.0, 35.5)	100.0
HPV11	4.4 (2.8, 5.9)	75.6	--	--	4.4 (2.8, 5.9)	75.1	--	--
HPV40	13.0 (6.8, 27.2)	100.0	11.5 (9.1, 14.2)	100.0	16.8 (9.2, 44.6)	100.0	31.5 (13.0, 173.5)	98.2
HPV42	15.0 (11.6, 21.2)	100.0	19.4 (11.9, 32.2)	100.0	21.8 (12.4, 37.9)	100.0	33.0 (16.4, 66.6)	100.0
HPV44	15.3 (7.0, 28.5)	100.0	11.3 (7.2, 18.2)	94.9	40.6 (9.5, 195.6)	99.7	44.4 (7.2, 81.2)	63.7
HPV54	13.3 (10.0, 19.3)	100.0	15.0 (10.9, 26.9)	100.0	16.8 (12.7, 25.9)	100.0	99.4 (32.6, 470.3)	96.2
All Woman-Level	15.6 (13.2, 20.7)	100.0	19.2 (13.3, 29.8)	100.0	34.3 (24.0, 50.2)	100.0	33.4 (18.3, 57.8)	100.0
Any HPV-Level[a]	13.9 (11.9, 16.5)	100.0	28.9 (20.7, 38.9)	100.0	23.2 (17.0, 32.3)	100.0	80.6 (57.2, 117.3)	100.0
Subgenus 2								
HPV16	28.5 (20.2, 39.7)	100.0	21.2 (10.9, 71.9)	99.9	44.6 (30.8, 66.3)	100.0	24.8 (11.6, 112.6)	99.5
HPV18	12.5 (9.3, 18.2)	100.0	40.4 (11.8, 148.8)	99.5	13.5 (9.9, 20.7)	100.0	109.1 (23.4, 285.6)	87.0
HPV26	--	--	--	--	--	--	--	--
HPV31	15.5 (11.5, 21.7)	100.0	11.3 (8.5, 19.9)	100.0	21.2 (14.4, 42.8)	100.0	15.9 (13.2, 79.5)	100.0
HPV33	9.9 (4.9, 38.2)	97.6	6.5 (4.6, 8.6)	97.8	9.9 (4.8, 38.2)	97.4	6.5 (4.6, 8.5)	97.8
HPV34	9.3 (6.7, 14.0)	100.0	5.9 (5.8, 6.0)	100.0	9.3 (6.7, 14.0)	100.0	--	--
HPV35	15.7 (6.2, 47.6)	89.8	16.6 (7.7, 22.5)	98.5	15.7 (6.2, 47.6)	90.6	36.8 (18.5, 58.2)	68.4
HPV39	14.2 (11.4, 18.4)	100.0	17.5 (10.0, 35.0)	100.0	25.7 (14.3, 43.9)	100.0	39.6 (14.9, 107.3)	100.0
HPV45	9.4 (6.7, 12.5)	100.0	9.4 (6.2, 14.5)	100.0	23.1 (8.1, 80.6)	100.0	212.4 (25.9, 298.4)	63.6
HPV51	16.0 (13.0, 20.7)	100.0	13.7 (9.8, 17.9)	100.0	25.8 (15.9, 41.6)	100.0	37.6 (15.1, 117.8)	99.9
HPV52	13.9 (10.3, 20.2)	100.0	15.4 (10.0, 27.0)	100.0	28.7 (17.5, 54.4)	100.0	17.2 (10.8, 33.7)	100.0
HPV53	18.5 (15.0, 22.6)	100.0	13.7 (10.7, 23.1)	100.0	34.2 (19.8, 66.3)	100.0	64.4 (26.5, 188.3)	100.0
HPV56	15.8 (9.9, 30.8)	100.0	10.7 (8.2, 15.2)	100.0	22.0 (11.8, 45.8)	100.0	11.8 (9.3, 34.4)	100.0
HPV58	18.3 (11.7, 30.6)	100.0	21.5 (15.4, 29.4)	99.9	21.4 (12.4, 41.0)	100.0	87.1 (22.3, 155.7)	63.2
HPV59	11.5 (9.2, 14.4)	100.0	13.7 (8.1, 21.3)	100.0	14.6 (10.7, 20.8)	100.0	64.4 (16.3, 231.0)	99.6
HPV66	10.9 (8.7, 13.3)	100.0	9.7 (8.0, 11.6)	100.0	13.4 (9.4, 20.8)	100.0	11.9 (9.6, 17.5)	100.0
HPV67	10.7 (8.6, 13.3)	100.0	10.9 (9.1, 13.6)	100.0	13.1 (10.1, 17.6)	100.0	18.3 (12.0, 35.3)	100.0
HPV68	29.6 (15.6, 66.3)	100.0	14.0 (7.9, 52.1)	98.0	45.9 (21.3, 133.2)	99.8	24.8 (8.5, 82.6)	91.4
HPV69	--	--	--	--	--	--	--	--
HPV70	18.0 (4.7, 32.0)	95.2	14.4 (6.2, 23.2)	99.7	47.8 (17.4, 111.9)	65.7	--	--
HPV73	11.3 (7.7, 16.9)	100.0	11.0 (8.8, 13.4)	100.0	19.4 (10.9, 35.4)	100.0	15.6 (11.8, 26.5)	100.0
HPV82	7.1 (5.1, 9.6)	100.0	11.9 (7.2, 23.7)	100.0	8.0 (5.4, 11.4)	100.0	15.0 (8.0, 41.1)	99.5
All Woman-Level	30.9 (23.9, 41.4)	100.0	21.5 (13.6, 33.4)	100.0	77.0 (57.0, 98.9)	100.0	90.0 (39.1, 185.4)	100.0
Any HPV-Level[a]	15.5 (14.1, 17.8)	100.0	25.4 (18.2, 31.9)	100.0	27.9 (23.5, 32.7)	100.0	82.5 (61.0, 103.3)	100.0
Subgenus 3								
HPV61	24.0 (11.4, 73.2)	100.0	23.1 (9.8, 66.7)	99.9	28.2 (12.9, 103.6)	99.9	58.3 (16.0, 289.7)	96.6
HPV62	20.5 (15.8, 28.6)	100.0	13.1 (9.4, 17.0)	100.0	52.0 (27.7, 103.2)	100.0	20.3 (15.3, 62.2)	100.0
HPV71	8.2 (6.5, 9.9)	100.0	--	--	--	--	--	--
HPV72	--	--	--	--	--	--	--	--
HPV81	12.6 (8.2, 27.4)	99.9	--	--	15.0 (13.6, 39.2)	98.6	--	--
HPV83	26.6 (10.9, 85.4)	100.0	10.4 (7.6, 20.8)	100.0	63.7 (13.7, 304.4)	97.7	11.2 (8.1, 32.4)	99.9

HPV84	11.0 (8.2, 14.8)	100.0	11.5 (8.6, 15.5)	100.0	17.2 (11.0, 28.5)	100.0	36.6 (16.7, 71.8)	100.0
HPV89	12.3 (9.9, 15.3)	100.0	14.4 (11.7, 17.3)	100.0	39.1 (18.8, 65.5)	100.0	47.8 (22.0, 107.4)	100.0
All Woman-Level	18.4 (15.8, 23.8)	100.0	15.3 (13.1, 18.5)	100.0	55.7 (38.5, 77.5)	100.0	26.1 (18.1, 65.0)	100.0
Any HPV-Level[a]	14.9 (12.6, 18.2)	100.0	22.8 (17.1, 29.6)	100.0	34.7 (24.3, 47.3)	100.0	72.2 (46.9, 109.5)	100.0
All 36 Types								
All Woman-Level	32.3 (24.9, 43.8)	100.0	41.3 (21.7, 78.4)	100.0	104.1 (77.3, 137.8)	100.0	118.8 (49.4, 269.3)	100.0
Any HPV-Level[a]	15.0 (13.7, 16.5)	100.0	26.3 (20.1, 31.6)	100.0	28.6 (24.1, 32.7)	100.0	84.5 (63.7, 99.9)	100.0

Abbreviations: CI, confidence interval; HPV, human papillomavirus; reps., replications.

-- indicates an insufficient number of women were at risk (i.e., 0) or experienced the outcome (i.e., 0 or 1) to estimate this value.

[a] 95% CIs for mean times to clearance determined by woman-cluster resampling bootstraps.



Abbreviations: HPV, human papillomavirus; mos., months (1 month = 30.437 days).

M1-Figure S1. Analytical framework for liberal clearance of infection present at baseline.

i. Woman-level analysis for a given HPV type: Woman must be positive for HPV*x* at baseline. She has a liberal clearance at 24 months, when she tests negative for HPV*x*.

ii. Woman-level analysis for grouped HPV types *x*, *y*, and *z*: Woman must be positive for one or more types at baseline. She never clears all three types at a single visit, so she is right-censored (24 months).

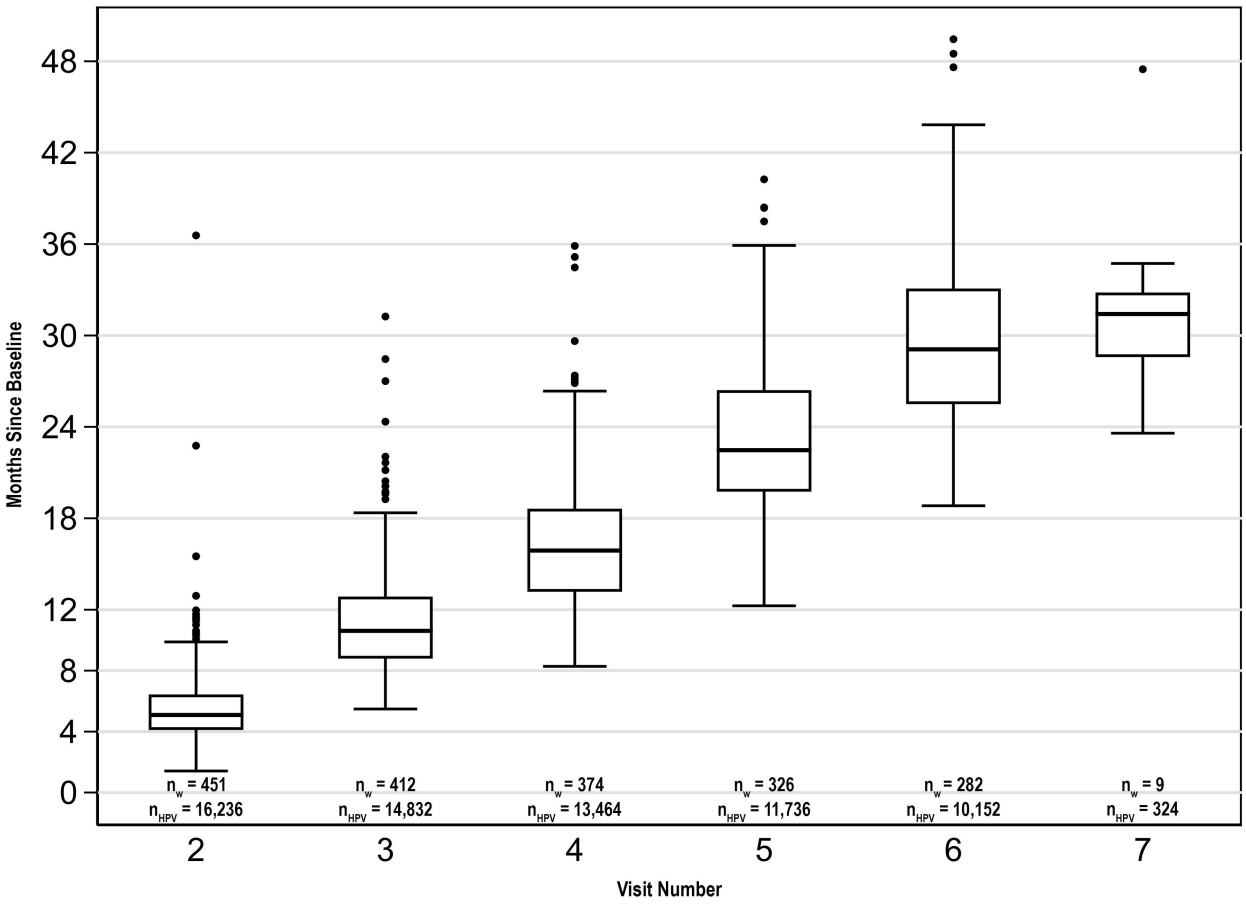
iii. HPV-level analysis for grouped HPV types *x, y,* and *z*: HPV types must be present at baseline. There will be a liberal clearance each first time woman tests negative for any type following a visit where she was positive for the same type. HPV*x* and HPV*z* have liberal clearances at 24- and 18-months, respectively; HPV*y* is right-censored (24 months).

Symbol Legend:

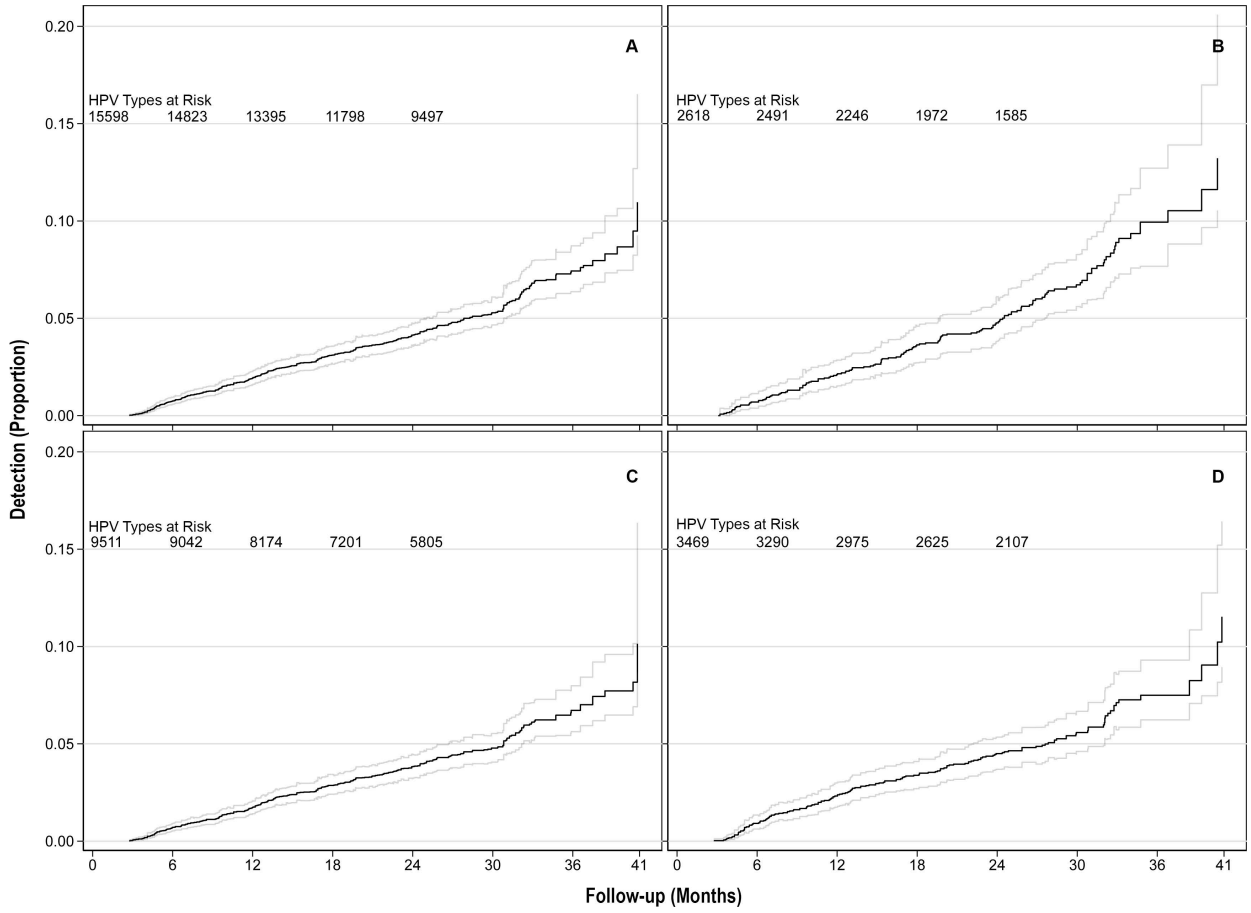
⚥ : Debut of woman's sexual relationship with a male partner occurred 0-6 months pre-baseline.

⬇ : Data are right-censored.

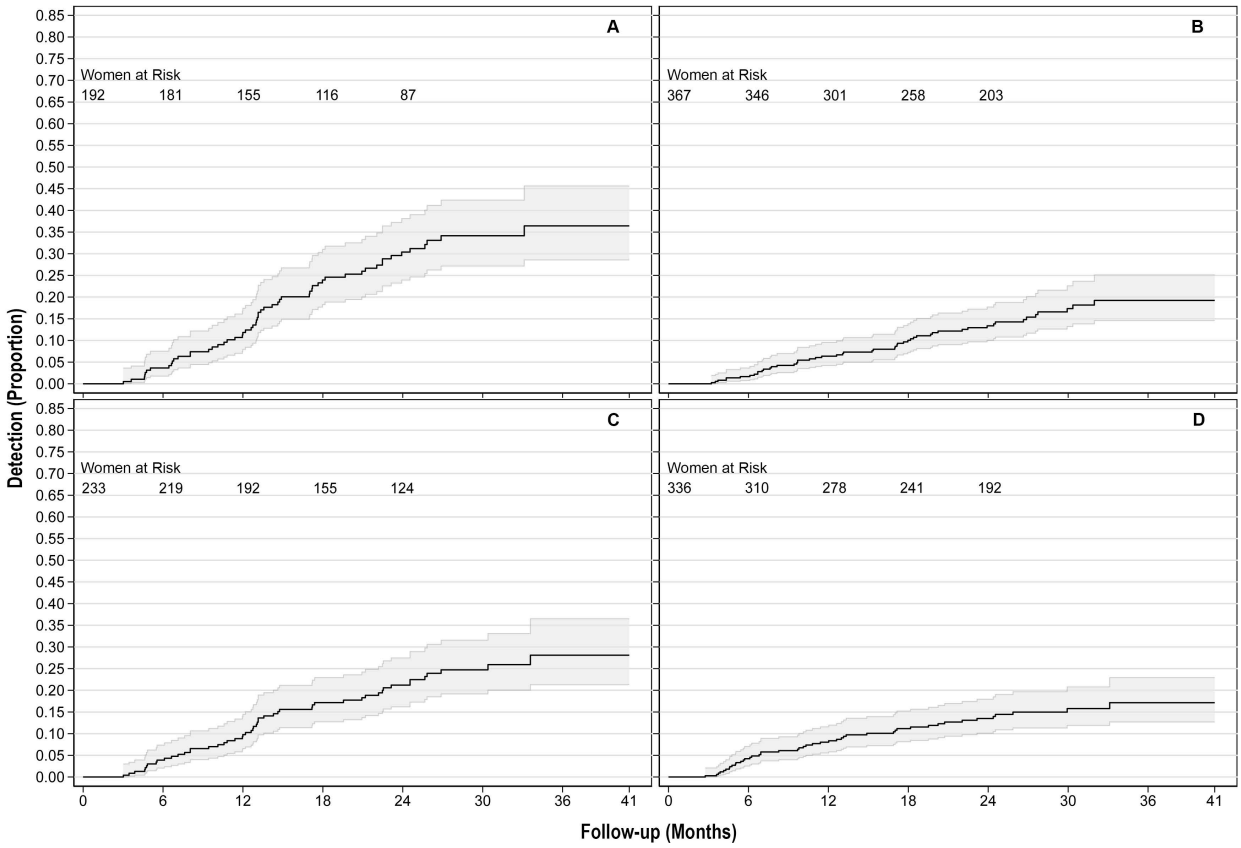
⟹ : Time to discrete event of interest. Gradient arrows indicate that biological clearance occurred at an unknown time before the clearance event at the arrowhead. Solid blue arrow counts time at risk contributed before censorship at the arrowhead.



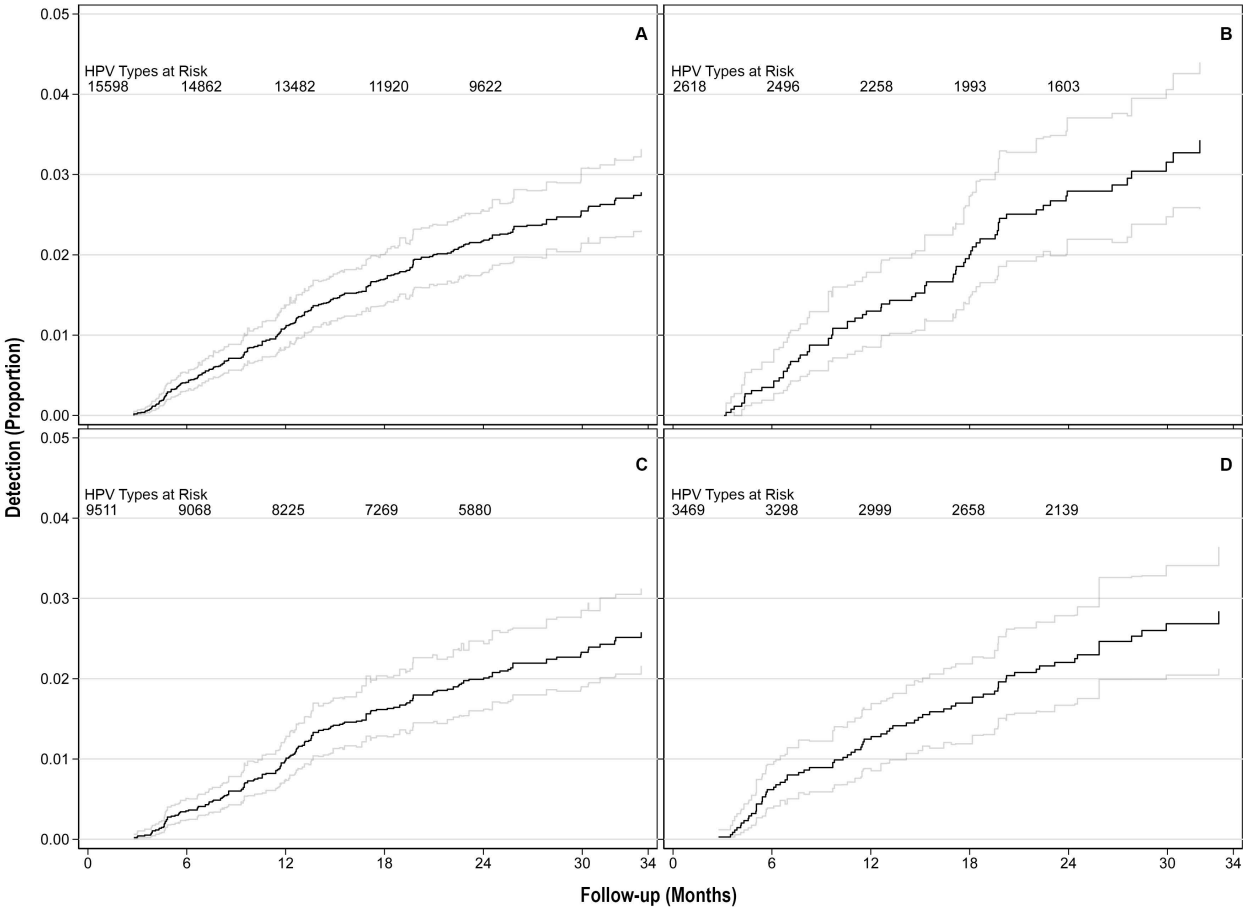
M1-Figure S2. Months post-baseline at which women attended follow-up visits. Sample size per visit provided for woman- (n_w) and HPV- (n_{HPV}) level prevalence analyses. Protocol-designated times for visits 2-6 were 4-, 8-, 12-, 18- and 24-months post-baseline; visit 7 was auxiliary.



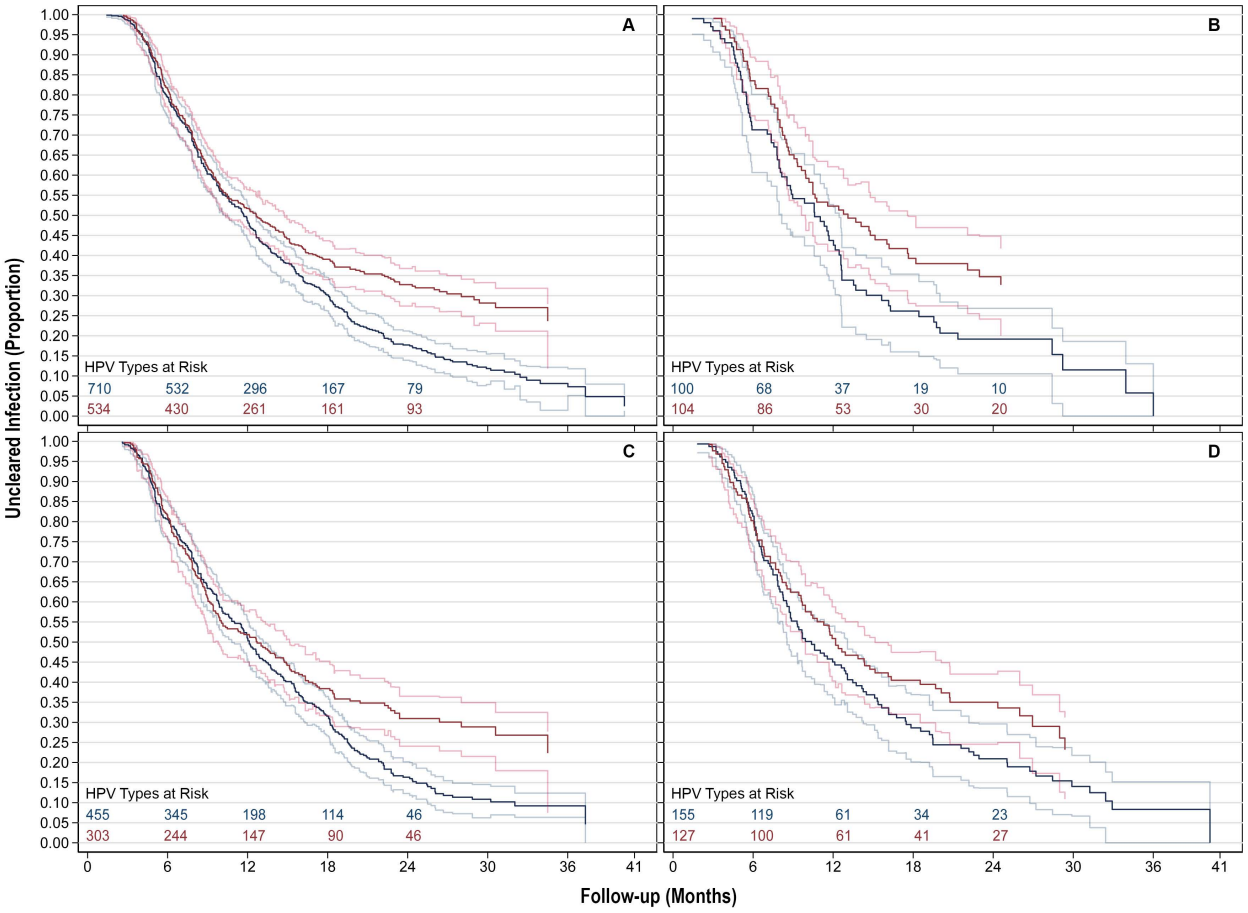
M1-Figure S3. Single detection of incident infection with any (A) HPV type, (B) subgenus 1, (C) subgenus 2, and (D) subgenus 3 type, at the HPV-level. Risk tables were extracted from standard Kaplan-Meier plots and appended to the above plots, which incorporate bootstrap-based confidence intervals.



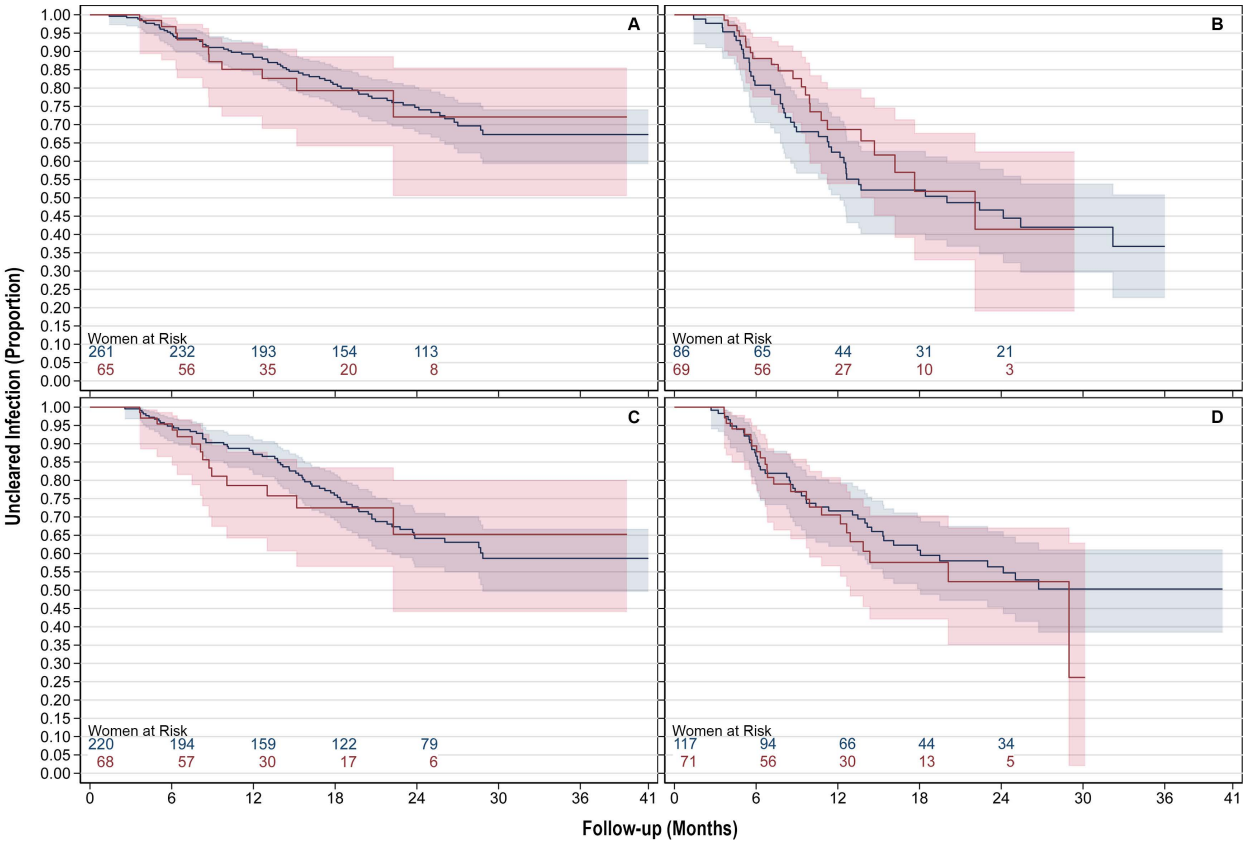
M1-Figure S4. Double detection of incident infection with any (A) HPV type(s), (B) subgenus 1, (C) subgenus 2, and (D) subgenus 3 type(s), at the woman-level.



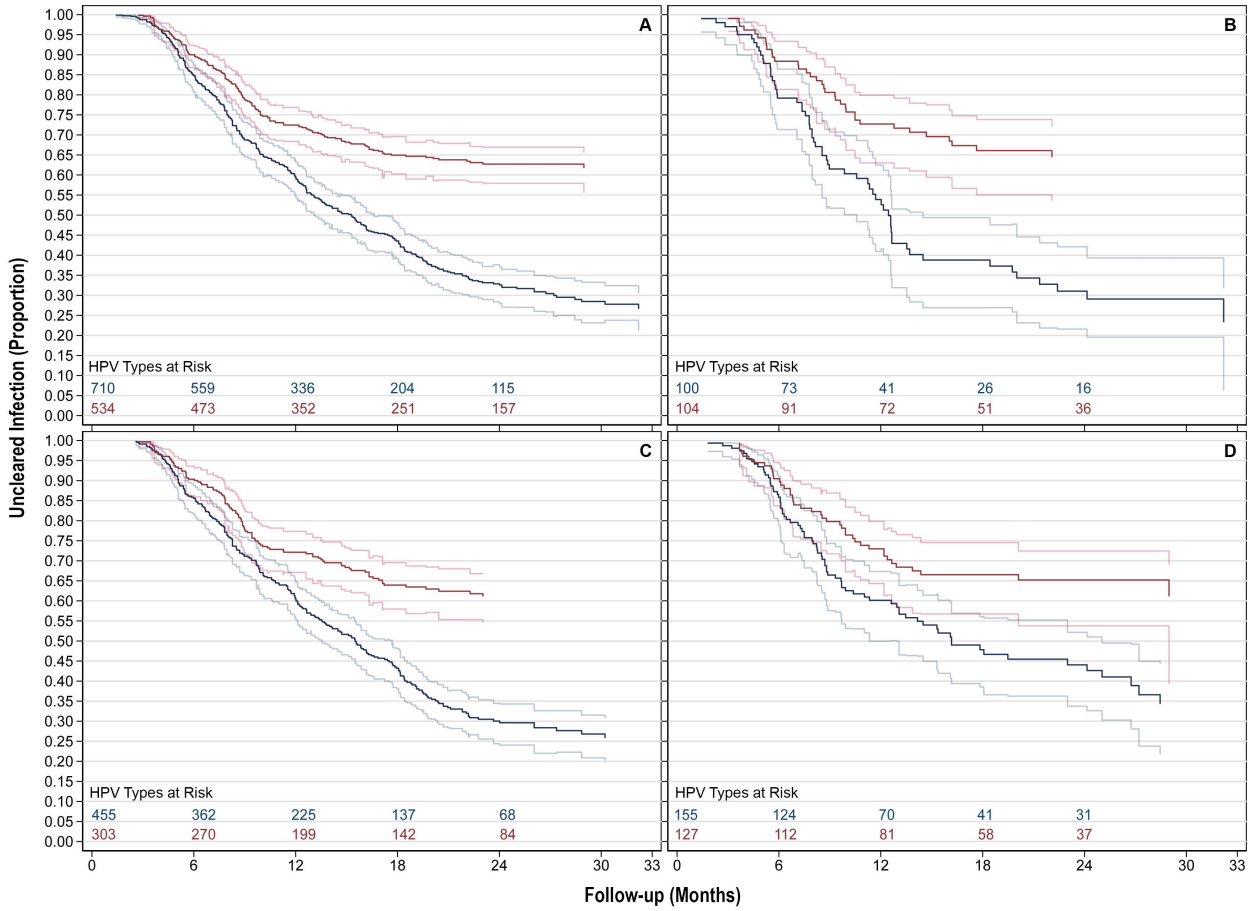
M1-Figure S5. Double detection of incident infection with any (A) HPV type, (B) subgenus 1, (C) subgenus 2, and (D) subgenus 3 type, at the HPV-level. Risk tables were extracted from standard Kaplan-Meier plots and appended to the above plots, which incorporate bootstrap-based confidence intervals.



M1-Figure S6. Liberal clearance of any (A) HPV type, (B) subgenus 1, (C) subgenus 2, and (D) subgenus 3 type for incident infections (red) and infections present at baseline (blue), at the HPV-level. Risk tables were extracted from standard Kaplan-Meier plots and appended to the above plots, which incorporate bootstrap-based confidence intervals.



M1-Figure S7. Conservative clearance of all (A) HPV type(s), (B) subgenus 1, (C) subgenus 2, and (D) subgenus 3 type(s) for infections present at baseline (blue) and incident infections (red), at the woman-level.



M1-Figure S8. Conservative clearance of any (A) HPV type, (B) subgenus 1, (C) subgenus 2, and (D) subgenus 3 type for incident infections (red) and infections present at baseline (blue), at the HPV-level. Risk tables were extracted from standard Kaplan-Meier plots and appended to the above plots, which incorporate bootstrap-based confidence intervals.

M1-Addendum S1. Woman-Level Analyses of Given HPV Types: For each outcome, we performed 36 woman-level analyses of individual HPV types, with one analysis for each HPV type tested. Each analysis of a given HPV type incorporated women's longitudinal positivity statuses for one individual type of HPV.

M1-Addendum S2. Woman-Level Analyses of Grouped HPV Types: For each outcome, we performed 4 woman-level analyses of grouped HPV types, with one analysis for each subgenus, and one analysis including all 36 HPV types. These analyses treat each woman's longitudinal HPV status as a composite. A woman was considered HPV-positive when she tested positive for one or more of the HPV types included in the group of interest, and HPV-negative only when she tested negative for all those types.

M1-Addendum S3. HPV-Level Analyses of Grouped HPV Types: For each outcome, we performed 4 HPV-level analyses of grouped HPV types, with one analysis for each subgenus, and one analysis including all 36 HPV types. These analyses handle women's longitudinal HPV statuses for each unique HPV type in the group of interest separately. In so doing, HPV-level analyses can account for a woman's simultaneous positivity and negativity for multiple different HPV types.

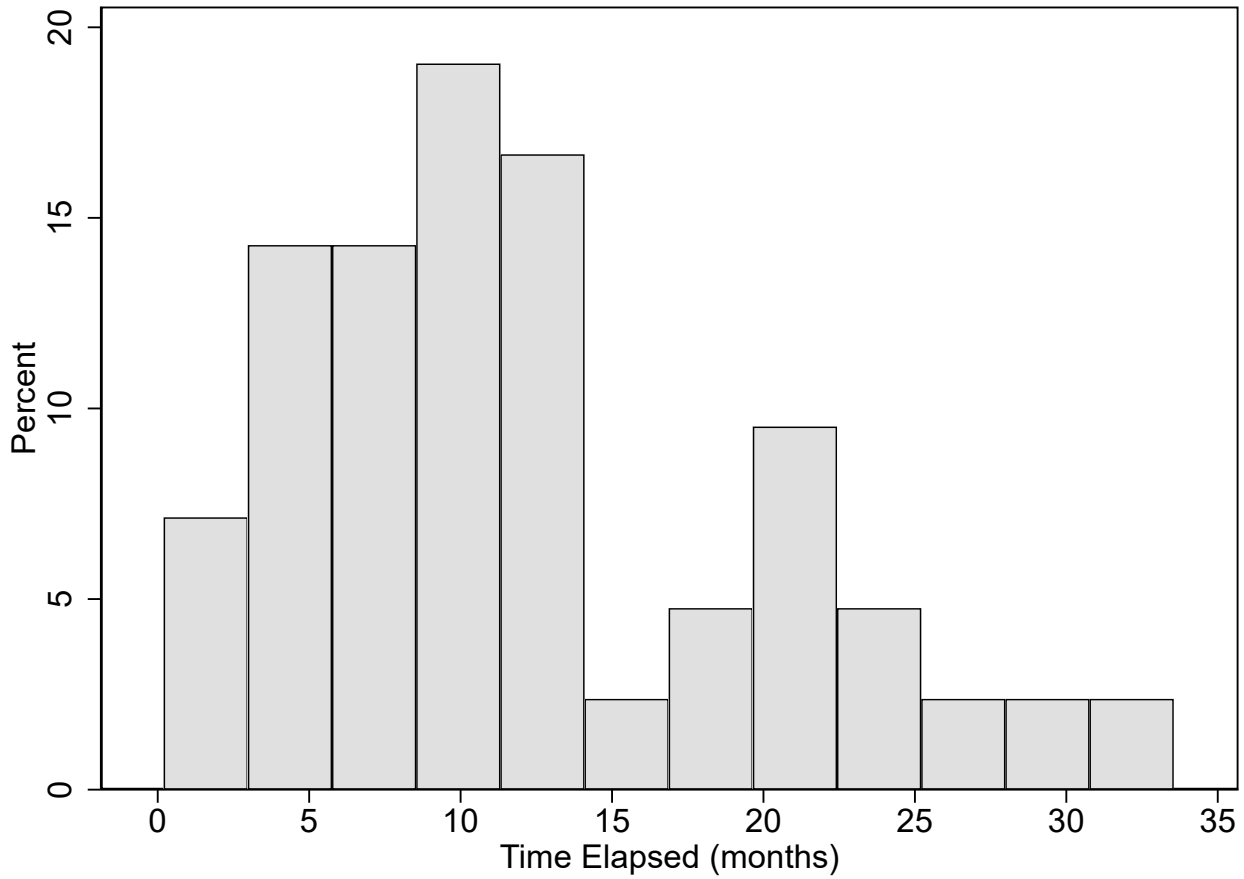
M2-Table S1. Agreement between sample collection sites and visits in males for type-specific HPV positivity, overall and by subgenus.[a]

	Penile and Scrotal Samples at Baseline					Penile and Scrotal Samples at Follow-up					Baseline and Follow-up: Combined Genital Site(s)				
	--	-+	+-	++	Kappa[b]	--	-+	+-	++	Kappa[b]	--	-+	+-	++	Kappa[b]
Male 1															
Overall	591	5	15	37	0.77	712	6	18	20	0.61	1154	18	27	61	0.71
Subgenus 1	98	1	3	6	0.73	116	1	5	4	0.55	190	3	6	11	0.69
Subgenus 2	362	1	11	22	0.77	435	4	13	10	0.52	706	12	15	37	0.71
Subgenus 3	131	3	1	9	0.80	161	1	0	6	0.92	258	3	6	13	0.73
Male 2															
Overall	497	4	22	17	0.54	168	1	2	9	0.85	999	37	26	54	0.60
Subgenus 1	82	0	4	4	0.65	29	0	0	1	1.00	164	4	4	14	0.75
Subgenus 2	303	3	15	9	0.47	100	1	2	7	0.81	609	25	17	31	0.56
Subgenus 3	112	1	3	4	0.65	39	0	0	1	1.00	226	8	5	9	0.55

Abbreviation: HPV, human papillomavirus.

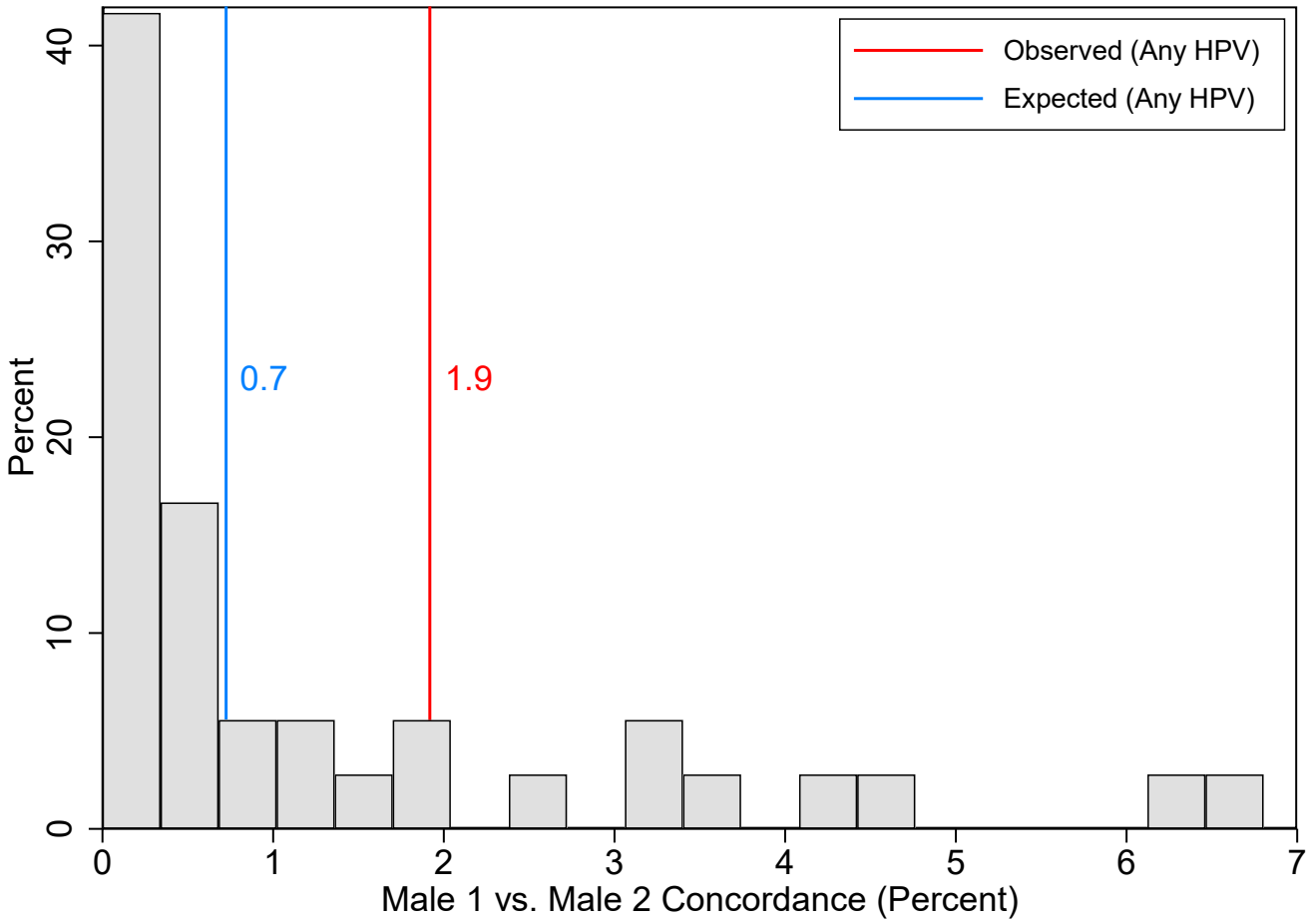
[a] Subgenus 1 includes low oncogenic risk mucosal HPVs 6, 11, 40, 42, 44, and 54; subgenus 2 includes high oncogenic risk mucosal HPVs 16, 18, 26, 31, 33, 34, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73 and 82; and subgenus 3 includes commensal mucocutaneous HPVs 61, 62, 71, 72, 81, 83, 84 and 89 [18, 19].

[b] Kappa values 0.41-0.60 indicate moderate, 0.61-0.80 substantial, and 0.81-1.00 almost perfect agreement [17].



M2-Figure S1. Distribution of time elapsed between male 1 last available sample and male 2 baseline sample within linked partnerships.

M2-Figure S1 Legend: While all male 2 provided a baseline genital sample, male 1 follow-up visits did not begin until October 2006. As such, we measured the time between males 1 and 2 providing genital samples based on the last sample male 1 provided. When male 1 provided a follow-up sample, we measured the time between male 1 follow-up and male 2 baseline; otherwise, we measured the time between male 1 baseline and male 2 baseline.



M2-Figure S2. Expected human papillomavirus (HPV) concordance between male 1 and male 2.

M2-Figure S2 Legend: Distribution of expected concordance for 36 individual HPV types. Assuming that the HPV positivity of males 1 and 2 is independent, the number of infections for which males 1 and 2 are expected to be concordant is equal to the product of the infection prevalence, divided by the total number of detectable infections (i.e., $\frac{P_{HPVx,Male1} \times P_{HPVx,Male2}}{T_{HPVx}}$).