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Human papillomavirus incidence and transmission by vaccination status among heterosexual couples

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ABSTRACT

Background: Understanding human papillomavirus (HPV) transmission dynamics within couples is necessary for optimal vaccine catch-up strategies. We used data from the Transmission Reduction and Prevention with HPV Vaccination (TRAP-HPV) study to estimate sex-specific incidence and transmission rates.

Methods: The TRAP-HPV study enrolled (2014–2022) new (≤6 months) heterosexual couples aged 18+ in Montreal, Canada. The study employed a 2 × 2 factorial design. Participants (n = 308) were randomized into four groups: neither partner vaccinated against HPV, only the male partner vaccinated against HPV, only the female partner vaccinated against HPV, or both partners vaccinated against HPV. Genital samples, collected at 0, 2, 4, 6, 9, and 12 months, were genotyped for 36 HPV types. We performed time-to-event analyses for vaccine-targeted HPVs (6/11/16/18/31/33/45/52/58) and HPVs phylogenetically related (35/39/44/59/67/68/70) and unrelated (26/34/40/42/51/53/54/56/61/62/66/69/71/72/73/81/82/83/84/89) to vaccine-targeted types, using type-specific HPV infections as the unit of analysis.

Results: Participants had a mean age of 25.5 years (SD 6.0), and a median of 6 (IQR: 2–15) lifetime sexual partners. Among males, incidence rates (in events/1000 months) were 0.99 (95 % CI: 0.17–3.07) and 1.67 (95 % CI: 0.75–3.51) in the two groups with vaccinated males versus 2.42 (95 % CI: 0.97–7.63) and 3.35 (95 % CI: 1.95–6.30) in the groups with unvaccinated males. Results were similar for the three HPV groups.

Conclusions: There was no consistent pattern of protection against incident HPV detection in females and no indication that recent vaccination was associated with lower transmission in discordant couples or with protection for one's partner. Findings should not be generalized to younger populations.

1. Introduction

Human papillomavirus (HPV) infections are common, with an estimated worldwide prevalence of 11.7 % [1]. Research on the population from the pre-vaccine era indicates that many sexually active adults contracted at least one HPV infection over the course of their lives [2]. There are over 40 types of HPV that can infect the genital mucosal epithelium [3], and co-infections with more than one HPV type are common [4,5]. Many HPV infections are asymptomatic, and most become undetectable and/or are cleared by the immune system within two years [4,6]. However, persistent infections with high-risk HPV types (particularly HPVs 16 and 18) can lead to oncogenesis [1,4,7]. Infections with low-risk HPVs (6 or 11) are the cause of genital warts and recurrent respiratory papillomatosis [4].

The Merck Gardasil quadrivalent vaccine protects against HPVs 6, 11, 16 & 18 [8,9], whereas Gardasil 9 (a nine-valent vaccine) protects against an additional five oncogenic types (HPVs 31/33/45/52/58) [10]. HPV vaccination is effective in preventing vaccine-targeted type infections in both females and males, [10–13] especially when administered at a young age and before exposure to HPV. Vaccination after the

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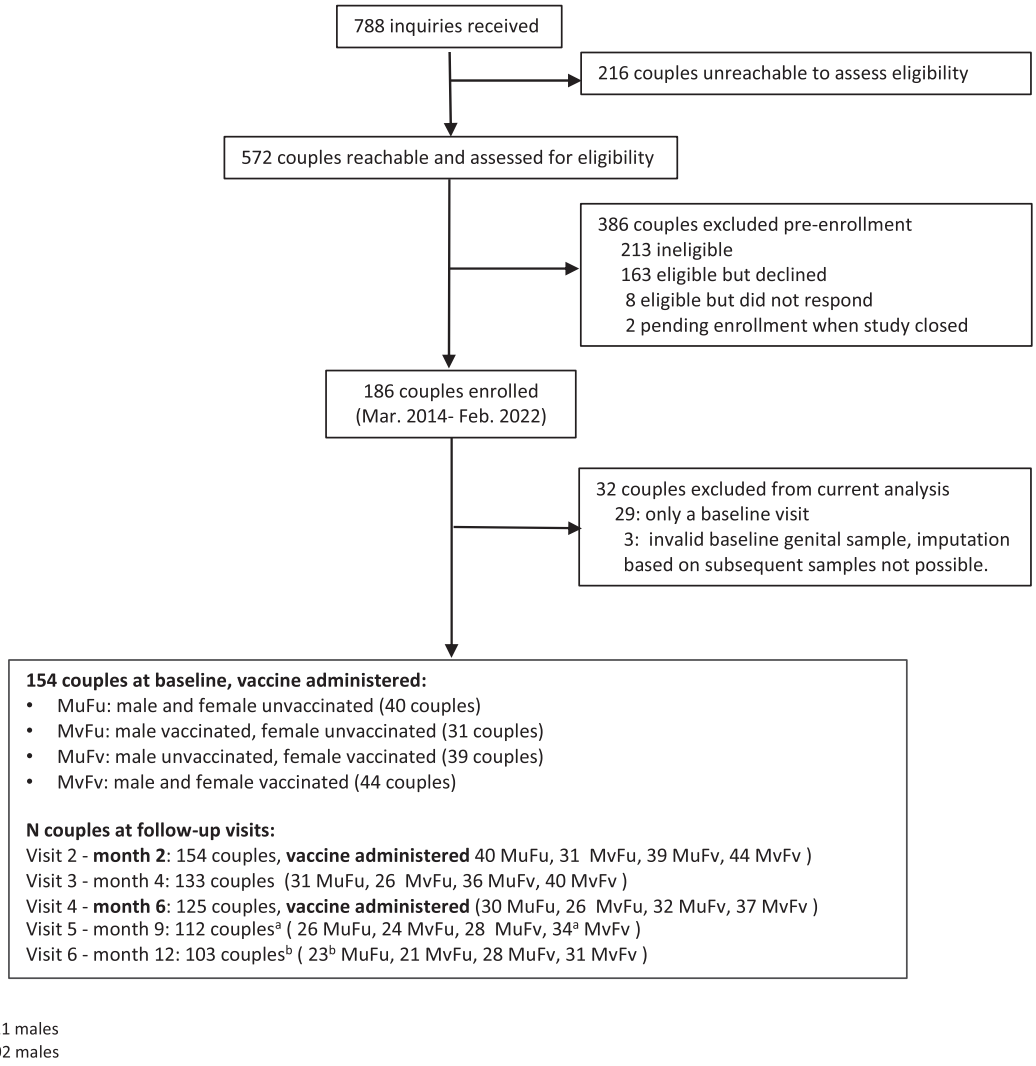

Fig. 1. Enrollment, randomization, and analytical sample in the TRAP-HPV study. In May 2022, the study protocol was amended to make visit 5 the final visit. This shortened follow-up duration affected only three couples.

onset of sexual activity can still be beneficial, especially with Gardasil 9, as individuals may not yet have been exposed to all the vaccine-targeted HPV types [14].

Previous research has found sex-specific differences in the epidemiology and natural history of HPV infections; the rates of new infections remain relatively constant throughout adulthood in males, whereas in females, these are highest in young adults <25 years and then decline [1,15,16] with a second smaller peak in middle age [3,6]. Many seemingly incident detections of HPV in middle-aged females may be re-detections of latent infections [6,17,18]. It is unknown whether vaccination can reduce this re-emergence of latent infections [19].

Studies on HPV acquisition or prevention are often conducted with individuals as the unit of observation. However, as HPV is a sexually transmitted infection, optimal vaccination strategies require understanding transmission dynamics within couples [20,21]. Sexual contact with a new partner is a recognized risk factor for incident HPV infection [4], and the transmission of HPV is most likely to occur early in a relationship [22,23]. Yet, couple-based studies tend to include participants who have been together for a considerable length of time or do not report information on the duration of the relationship [21], making it challenging to elucidate transmission patterns. Another challenge to understanding the effects of vaccination on transmission dynamics is that HPV vaccination is often self-reported in epidemiological studies.

We previously showed, using data from an observational cohort study, that self-reported vaccination reduces transmission within couples [24]. A preliminary cohort analysis from a randomized controlled trial by our group, the Transmission Reduction and Prevention with HPV Vaccination (TRAP-HPV) designed to determine the efficacy of HPV vaccination in reducing transmission of HPV to the partners of vaccinated participants [27], found a lower risk of incident infections in vaccinated participants but no evidence of protection for one's partner [20]. Here, we used data from the final enrolled sample of the TRAP-HPV study to estimate sex-specific patterns of HPV transmission in newly formed heterosexual couples according to the four arms of the study, i.e., considering the vaccination status of the male and female partners.

2. Methods

2.1. Study design and procedures

Details of the TRAP-HPV study (registered at ClinicalTrial.gov; ID number: NCT01824537) have been described previously [20,25]. Briefly, the study enrolled couples in Montreal, Canada (January 2014–February 2022) if they fulfilled the following inclusion criteria: participants were cisgender, heterosexual couples (aged 18+) who had not received the intervention vaccine, had no anogenital cancer history, had been together for six months or less, were planning to stay in the

Montreal area for at least a year and to have ongoing sexual contact, and were not pregnant or planning to become pregnant in the next year [25]. The first couple was enrolled in March 2014 and the last follow-up visit occurred in December 2022. The study employed a 2 × 2 factorial design; participants were randomized individually to receive the intervention HPV vaccine (Gardasil before July 15, 2015, or Gardasil 9 thereafter) or a hepatitis A vaccine as the active control (Havrix before June 12, 2018, or Avaxim thereafter). This randomization created four trial arms in terms of who received the intervention vaccine: neither partner (M_uF_u), only the male partner (M_vF_u), only the female partner (M_uF_v), and both partners (M_vF_v). At the end of follow-up, participants were informed which vaccine they had received and offered the other vaccine. Genital samples were collected at enrollment and at 2, 4, 6, 9, and 12 months. Study procedures were interrupted by the COVID-19 pandemic, resulting in more than 12 months follow-up time for some participants; this affected control and intervention-vaccinated participants equally.

Participants were requested not to engage in sexual activity for at least 48 h before each clinic visit. Female genital samples were self-collected after receiving written and verbal instructions from a research nurse and in accordance with a previously validated protocol [26–28]. Male genital samples were collected by a research nurse in accordance with a previously validated protocol [29,30]. At each visit, participants individually filled out self-administered electronic questionnaires, providing information on sociodemographic factors, sexual behaviors, and sexual health history.

The Institutional Review Boards of McGill University (A04-M37-12A), Concordia University (30001405), and Centre Hospitalier de l'Université de Montréal (2014–2019, CE 13.016) approved the TRAP-HPV study. Written informed consent was collected from all participants.

2.2. HPV genotyping

HPV genotyping was done by polymerase chain reaction (PCR). Most samples (83 %) were assayed for 36 HPV genotypes (6/11/16/18/26/31/33/34/35/39/40/42/44/45/51/52/53/54/56/58/59/61/62/66/67/68/69/70/71/72/73/81/82/83/84/89) via the Linear Array HPV Genotyping Test (Roche Diagnostic, Laval, Canada). Due to unavailability of Linear Array reagents, later samples (17 %) were tested via the Anyplex II HPV28 Detection assay (Seegene, Seoul, Korea) for 28 HPV types (6/11/16/18/26/31/33/35/39/40/42/43/44/45/51/52/53/54/56/58/59/61/66/68/69/70/73/82). Both assays have very good agreement, with Anyplex II being more likely to detect multiple genotypes in the same sample [31]. Regardless of the assay used, co-amplification of the human β-globin gene was conducted to determine if samples were valid (i.e., contained sufficient intact human DNA) for HPV genotyping. Additionally, the Anyplex II samples were run with positive and negative controls from the manufacturer.

2.3. Statistical analysis

As shown in Fig. 1, the current analysis includes 82.8 % of the enrolled participants, consisting of 154 couples who had i) at least one follow-up visit, and ii) valid baseline genital samples from both partners, or imputation was possible based on subsequent visits in case a baseline genital sample was invalid. For females and males within each study arm, we calculated, via time-to-event and Kaplan–Meier analyses, the incidence and transmission rates (and their 95 % confidence intervals, CI) in events/1000 infection-months at risk (each participant could contribute time at risk for up to 36 type-specific HPV-level infections). Participants contributed time at risk for incidence of type-specific HPV-level infections if they had not previously tested positive for that HPV type (Supplementary Fig. 1A). Participants contributed time at risk for transmission if they had not previously tested positive for that HPV type and their partner had previously tested positive for that HPV type (Supplementary Fig. 1B).

We considered three groups of HPVs: (1) vaccine-targeted types, against which we would expect to see protection from recent vaccination; (2) types phylogenetically related (HPVs 35/39/44/59/67/68/70) to vaccine-targeted types [32], against which we might expect to see a limited amount of protection from recent vaccination [33,34]; and (3) other mucosotropic HPV types phylogenetically unrelated to the previous two groups (HPVs 26/34/40/42/51/53/54/56/61/62/66/69/71/72/73/81/82/83/84/89), against which we would not expect to see protection from recent vaccination. For the 9 HPV types detectable by Linear Array but not Anyplex II (HPVs 34/62/67/71/72/81/83/84/89), time at risk was included for samples tested via the former and truncated if later samples were tested via the latter assay. HPV 43, which is only detectable by Anyplex II, was not considered in the analyses.

Jackknife CIs are reported wherever possible to account for intra-participant correlation; if there were insufficient events, exact Fisher's 95 % CIs were calculated using WinPepi (version 11.65, J.H. Abramson, 2016). We conducted a sensitivity analysis, restricting to couples wherein both partners reported no outside sexual contact for the duration of their relationship. Most analyses were conducted in Stata (version 18.0, StataCorp LLC., TX).

3. Results

Table 1 presents baseline characteristics of participants by sex and vaccination status; These did not vary markedly between the groups. Overall, the mean age was 25.5 years (SD 6.0). Almost 50 % of participants were Canadian born, with 7.5 % born in the US and 42.8 % born elsewhere. The majority of participants had some post-secondary education, with only 17.5 % reporting high school as their highest level of education. Most had never been smokers, while 21.4 % and 7.8 % were former or current smokers, respectively. The median number of lifetime vaginal sexual partners was 6 (interquartile range: 2–15), and the median age at coitarche was 18 years (interquartile range: 16–19 years). The median time since coitarche was 5.8 years (interquartile range: 2.7–10.5 years). Overall, 43.5 % of participants were positive for at least one HPV type at baseline, 17.9 % were positive for one or more vaccine-preventable HPV types, 13 % were positive for one or more HPV types that are phylogenetically related to vaccine-preventable HPV types, and 39 % were positive for one or more HPV types phylogenetically unrelated to vaccine-preventable HPV types. Female participants were, on average, slightly younger than males, and ages were similar between vaccinated and unvaccinated participants. Positivity for any of the nine vaccine-targeted HPVs was slightly higher in females; 18.3 % and 19.3 % for vaccinated and unvaccinated participants, respectively; among males, it was 17.7 % and 16.0 % for vaccinated and unvaccinated participants, respectively. Unvaccinated males had a slightly lower prevalence of any HPV than those vaccinated (38.0 % vs 44.0 %). Conversely, unvaccinated females had a slightly higher prevalence of any HPV than vaccinated females (47.9 % vs 44.6 %). Unvaccinated males were less likely than vaccinated males to report having concurrent sexual partners (6.3 % vs 18.7 %). Vaccinated males included a higher percentage of participants without post-secondary education than unvaccinated males (28.0 % vs 15.2 %). Among vaccinated participants, 10.8 % of females and 14.7 % of males received the quadrivalent HPV vaccine (as opposed to the nine-valent) at baseline. However, only 6 % of vaccinated females and 8 % of vaccinated males received the quadrivalent vaccine exclusively throughout the study.

Table 2 shows the sex-specific incidence and transmission rates of the three outcomes among the four study arms. For vaccine-targeted HPV in females, there was no consistent pattern of protection (to oneself) against incident infection through recent vaccination. While the M_uF_v group had the lowest point estimate for the incidence rate (1.05, 95 % CI: 0.42, 3.45), the second lowest was in the M_uF_u group (1.40, 95 % CI: 0.51, 5.34), whereas the M_vF_u and M_vF_v groups had the highest point

Table 1
Baseline characteristics of participants in the TRAP-HPV study, overall and by sex and vaccine assignment.

Variables, n (%) unless otherwise indicated	Overall (n = 308)	Female		Male	
		Unvaccinated (n = 71)	Vaccinated[a] (n = 83)	Unvaccinated (n = 79)	Vaccinated[a] (n = 75)
Age, mean (SD)	25.5 (6.0)	24.2 (4.7)	25.4 (6.2)	25.7 (5.7)	26.7 (6.9)
Birth country					
Canada	152 (49.4)	39 (54.9)	41 (49.4)	36 (45.6)	36 (48.0)
United States	23 (7.5)	5 (7.0)	7 (8.4)	7 (8.9)	4 (5.3)
Elsewhere[b]	132 (42.9)	27 (38.0)	34 (41.0)	36 (45.6)	35 (46.7)
Missing	1 (0.3)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
Education					
High school	54 (17.5)	10 (14.1)	11 (13.3)	12 (15.2)	21 (28.0)
College or vocational training	55 (17.9)	10 (14.1)	15 (18.1)	16 (20.3)	14 (18.7)
University	198 (64.3)	51 (71.8)	57 (68.7)	50 (63.3)	40 (53.3)
Missing	1 (0.3)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Smoking status					
Never	216 (70.1)	52 (73.2)	60 (72.3)	59 (74.7)	45 (60.0)
Former[c]	66 (21.4)	13 (18.3)	16 (19.3)	16 (20.3)	21 (28.0)
Current	24 (7.8)	6 (8.5)	6 (7.2)	3 (3.8)	9 (12.0)
Missing	2 (0.6)	0 (0.0)	1 (1.2)	1 (1.3)	0 (0.0)
Concurrent sex partners[d]					
No	259 (84.1)	58 (81.7)	67 (80.7)	74 (93.7)	60 (80.0)
Yes	47 (15.3)	13 (18.3)	15 (18.1)	5 (6.3)	14 (18.7)
Missing	2 (0.6)	0 (0.0)	1 (1.2)	0 (0.0)	1 (1.3)
Number of lifetime sex vaginal partners, median (Q1, Q3)	6 (2, 15)	5 (2, 14)	6 (2, 20)	8 (3, 15)	7 (3, 16)
Age at coitarche, median (Q1, Q3)	18 (16, 19)	17 (16, 19)	17.5 (16, 19)	18 (16, 20)	18 (16, 19)
Years since onset of sexual activity, median (Q1, Q3)[e]	5.8 (2.7, 10.5)	4.8 (2.5, 9.4)	5.4 (2.5, 9.8)	6.0 (2.9, 10.3)	7.6 (3.1, 12.6)
Grouped HPV positivity[f]					
Vaccine-targeted (any 9vHPV)	55 (17.9)	13 (18.3)	16 (19.3)	14 (17.7)	12 (16.0)
Phylogenetically related to vaccine-targeted types	40 (13.0)	10 (14.1)	13 (15.7)	7 (8.9)	10 (13.3)
Phylogenetically unrelated to vaccine-targeted types	120 (39.0)	29 (40.8)	33 (39.8)	28 (35.4)	30 (40.0)
Any HPV	134 (43.5)	34 (47.9)	37 (44.6)	30 (38.0)	33 (44.0)

Abbreviations: HPV, human papillomavirus; Q1, first quartile; Q3, third quartile; SD, standard deviation.

[a] Participants (11 males and 9 females at baseline) received Gardasil up until July 8, 2015, after which they received Gardasil 9 (64 males and 74 females at baseline). Hence, among vaccinated participants, 10.8 % of females and 14.7 % of males received the quadrivalent HPV vaccine at baseline. Throughout the study, 5 vaccinated females (6 %) and 6 vaccinated males (8 %) received the quadrivalent vaccine exclusively.

[b] Includes: France, India, Iran, Brazil, China, Mexico, South Korea, Russian Federation & grouped regions: East Asia, Southeast Asia, MENA (Middle East and North Africa), Sub-Saharan Africa, Latin America, Europe, Central Asia, and Oceania.

[c] Includes participants who reported not being current smokers but reported smoking regularly in the past and/or reported having smoked at least 100 cigarettes in their lifetime.

[d] Any concurrent partners since the beginning of the relationship with TRAP-HPV partner, as reported at baseline.

[e] Age at baseline minus age at coitarche.

[f] Vaccine-targeted types include any of HPVs 6, 11, 16, 18, 31, 33, 45, 52, and 58. Phylogenetically related types include any of HPVs 35, 39, 44, 59, 67, 68, and 70. Phylogenetically unrelated types include any of HPVs 26, 34, 40, 42, 51, 53, 54, 56, 61, 62, 66, 69, 71, 72, 73, 81, 82, 83, 84, and 89. Any HPV includes any of 36 HPV types that were tested for: HPVs 6, 11, 16, 18, 26, 31, 33, 34, 35, 39, 40, 42, 44, 45, 51, 52, 53, 54, 56, 58, 59, 61, 62, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83, 84, and 89.

estimates for the incidence rates (1.58, 95 % CI: 0.55, 6.17 and 1.58, 95 % CI: 0.71, 4.25, respectively). The lowest point estimates for incidence rates were for phylogenetically related and unrelated HPVs in the M_uF_u group. For the vaccine-targeted HPVs in males, there was a pattern consistent with protection to self from recent vaccination; the point estimates for the incidence rates were lower in the groups with vaccinated males than those with unvaccinated males: 0.99 (95 % CI: 0.17, 3.07) and 1.67 (95 % CI: 0.75, 3.51) in the M_vF_u and M_vF_v groups, respectively, versus 2.42 (95 % CI: 0.97, 7.63) and 3.35 (95 % CI: 1.95, 6.30) in the M_uF_u and M_uF_v groups, respectively. As expected, this pattern was not seen for phylogenetically related and unrelated HPVs. For vaccine-targeted HPVs, there was no indication that recent vaccination of oneself or one's partner is associated with protection against transmission to females. The point estimate for the transmission rate was lowest in the group with neither partner vaccinated and highest in the group with both partners vaccinated (7.07, 95 % CI: 0.18, 39.37 vs 29.83, 95 % CI: 7.26, 145.53). For phylogenetically related HPVs, the point estimate for the transmission rate to females was also lowest in the group with neither partner vaccinated. There was also no consistent pattern indicating that recent vaccination of either oneself or one's partner is associated with lower transmission of vaccine-targeted HPV to males. Although the lowest point estimate for the transmission rate was observed in the M_vF_v group (0, 95 % CI: 0.00, 45.22), the second lowest was in the M_uF_u group (15.90, 95 % CI: 0.40, 88.61). Furthermore, the lowest point estimates for transmission rates for phylogenetically related and unrelated HPVs were also in the M_vF_v group.

Figs. 2 and 3 show the respective Kaplan–Meier failure curves for incidence and transmission across the 3 HPV groups within the 4 study arms. As expected, the M_vF_u group had a lower proportion of incident infections in males compared with females, while the M_uF_v group had a lower proportion of incident infections in females compared with males. However, these differences were slight, and the results were similar within the M_vF_u group for all three HPV groups. Contrary to expectations, the group with both partners vaccinated had a particularly high proportion of transmissions of vaccine-targeted HPV to females.

Restricting the analysis to couples who consistently reported no outside sexual contact (n = 87) showed similar findings of protection to oneself from recent vaccination in males but not in females (Supplementary Table S1). For transmission, the restricted sample had too few events to either support or contradict the findings from the main analysis.

Table 2
HPV incidence and transmission in female and male participants of the TRAP-HPV study, N = 308 (154 couples).

Vaccination assignment	Grouped HPV types[a]	Incidence						Transmission					
		Female			Male			Male-to-female			Female-to-male		
		Events	Time[b]	Rate[c] (95 % CI)	Events	Time[b]	Rate[c] (95 % CI)	Events	Time[b]	Rate[c] (95 % CI)	Events	Time[b]	Rate[c] (95 % CI)
Male and female unvaccinated n = 40 couples	**Vaccine-targeted**	5	3560.54	1.40 (0.51, 5.34)	8	3311.79	2.42 (0.97, 7.63)	1	141.54	7.07 (0.18, 39.37)[d]	1	62.88	15.90 (0.40, 88.61)[d]
	Related	1	2713.97	0.37 (0.01, 2.05)[d]	3	2552.65	1.18 (0.21, 17.18)	0	44.78	0 (0.00, 82.38)[d]	1	8.08	123.73 (3.09, 689.60)[d]
	Unrelated	12	7153.20	1.68 (0.94, 3.29)	15	6784.93	2.21 (1.35, 3.88)	4	172.82	23.15 (7.85, 76.83)	5	93.93	53.23 (28.79, 99.00)
Male vaccinated, female unvaccinated n = 31 couples	**Vaccine-targeted**	5	3172.26	1.58 (0.55, 6.17)	3	3034.10	0.99 (0.17, 3.07)	1	47.90	20.88 (0.52, 116.33)[d]	2	50.47	39.63 (4.79, 143.15)[d]
	Related	5	2305.25	2.17 (0.94, 6.02)	5	2219.67	2.25 (1.00, 6.10)	2	34.99	57.16 (11.98, 361.22)	2	38.11	52.48 (13.61, 271.55)
	Unrelated	22	6081.94	3.62 (1.88, 7.80)	17	5887.70	2.89 (1.49, 6.24)	9	147.78	60.90 (28.94, 141.46)	8	239.91	33.35 (14.26, 75.11)
Male unvaccinated, female vaccinated n = 39 couples	**Vaccine-targeted**	4	3793.67	1.05 (0.42, 3.45)	12	3581.69	3.35 (1.95, 6.30)	1	75.40	13.26 (0.33, 73.90)[d]	5	39.10	127.89 (41.84, 354.21)
	Related	3	2877.35	1.04 (0.34, 4.69)	6	2740.19	2.19 (1.05, 5.30)	1	62.49	16.00 (0.40, 89.17)[d]	2	65.25	30.65 (4.56, 245.92)
	Unrelated	22	7499.06	2.93 (1.67, 5.59)	26	7286.07	3.57 (2.28, 5.93)	2	131.78	15.18 (3.70, 108.35)	12	323.72	37.07 (20.92, 70.39)
Male and female vaccinated n = 44 couples	**Vaccine-targeted**	7	4431.81	1.58 (0.71, 4.25)	7	4189.61	1.67 (0.75, 3.51)	3	100.57	29.83 (7.26, 145.53)	0	81.58	0 (0.00, 45.22)[d]
	Related	9	3265.27	2.76 (1.43, 6.00)	10	3141.70	3.18 (1.58, 7.26)	2	77.50	25.80 (5.51, 199.62)	2	127.74	15.66 (3.65, 117.67)
	Unrelated	24	8712.42	2.75 (1.50, 5.63)	20	8307.32	2.41 (1.45, 4.26)	5	267.21	18.71 (7.33, 53.62)	7	333.80	20.97 (11.35, 40.69)

Abbreviations: HPV, human papillomavirus; TRAP-HPV, Transmission Reduction and Prevention with HPV Vaccination.

[a] Vaccine-targeted types include any of HPVs 6, 11, 16, 18, 31, 33, 45, 52, and 58. Phylogenetically related types include any of HPVs 35, 39, 44, 59, 67, 68, and 70. Phylogenetically unrelated types include any of HPVs 26, 34, 40, 42, 51, 53, 54, 56, 61, 62, 66, 69, 71, 72, 73, 81, 82, 83, 84, and 89.

[b] Indicates infection-months at risk. All analyses were at the HPV-level, meaning that each participant contributed time at risk for up to 36 HPV types. Participants contributed time at risk for incidence if they had not previously tested positive for that HPV type. If a participant tested positive for only 1 HPV type, they would no longer contribute time at risk for that particular type but would continue to contribute time at risk for the other 35 types. Participants contributed time at risk for transmission if they had not previously tested positive for that HPV type and their partner had previously tested positive for that HPV type.

[c] Rates represent events (incidence or transmission)/1000 infection-months at risk. Jackknife confidence intervals are reported wherever possible to account for intra-participant correlation.

[d] In instances where no events were observed, or there was an insufficient number of failures to calculate jackknife confidence intervals, exact Fisher's 95 % confidence intervals were used.

4. Discussion

We described the sex-specific incidence and transmission rates in the TRAP-HPV study according to the couple-level vaccination assignment group. The point estimates for incident detection rates among males are consistent with the pattern that we would expect to see if recent HPV-vaccination was associated with protection against incident HPV detections. However, there was quite a bit of overlap in the 95 % CIs. Thus, while the results for incidence in males are not inconsistent with a protective effect from recent vaccination, neither are they necessarily indicative of an effect. Overall, our findings are not consistent with protection, in terms of incidence or transmission, from recent vaccination for oneself or for one's partner. This is contrary to expectations and inconsistent with previous studies [20,24].

In this study, follow-up visits to detect incident infections started two months after the first vaccine dose. Previous research indicates that protection could have been observed by that time. Research from the Costa Rica vaccine trial, which found a persistent antibody response after one dose of the bivalent vaccine, showed that antibody titers at one month were above the subsequent plateau [35].

The previous cohort analysis of the TRAP-HPV data found indications of protection to oneself, reporting an overall hazard ratio (HR) of 0.47 (95 % CI: 0.23, 0.97) for incident infections of vaccine-targeted HPV types among vaccinated compared with unvaccinated participants, with HRs of 0.45 (95 % CI: 0.15, 1.35) and 0.51 (95 % CI: 0.19, 1.34) in females and males, respectively, for participants who had received at least one vaccination dose [20]. A couple of factors may have contributed to the differences between the previous and current findings. First, the previous analysis collapsed the study arms, resulting in larger groups with more events per group and, hence, more statistical power to detect an effect. Second, the follow-up time is longer in the current analysis, which could contribute to a different apparent distribution of events between the study arms.

There are few couple-based studies of HPV transmission and even

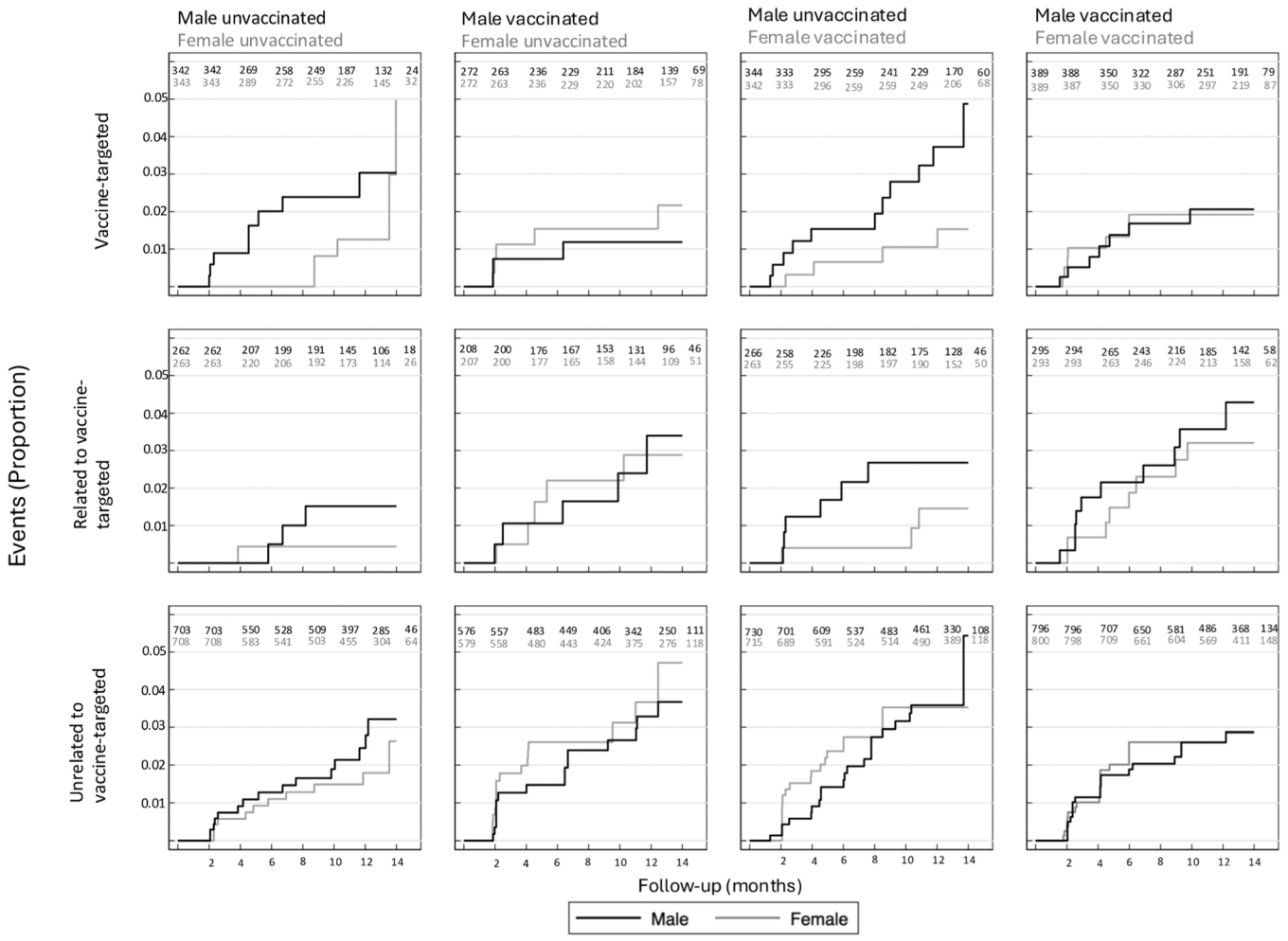

Fig. 2. Incidence of vaccine-targeted HPV types as well as that of HPV types phylogenetically related and unrelated to vaccine-targeted HPV types in males and females among the four vaccination assignment groups. Number of type-specific infections at risk is shown at the top of each graph for males (black) and females (grey). Each participant contributes up to 36 HPV types in total: 9 types for vaccine-targeted infections, 7 types for phylogenetically related, and 20 types for phylogenetically unrelated. These analyses were conducted at the HPV-level, meaning that risk-tables reflect the number or type-specific infections which could occur within each HPV category.

fewer which also considered vaccination [21]. One previous couple-based study which did consider vaccination was the HPV Infection and Transmission among Couples through Heterosexual activity (HITCH) cohort study (Montreal, Canada, 2005–2011) [24]. Participants were females aged 18–24 and their male partners aged 18 and over. Some of the female participants in the HITCH study elected to be vaccinated against HPV before or during the study, and self-reported vaccination of females reduced transmission of vaccine-targeted and phylogenetically related HPV types to their male partners [24]. However, the effect was entirely due to a reduced number of infections in vaccinated females, i.e., there was no evidence that vaccination reduced the transmissibility of pre-existing infections [24]. Several methodological characteristics inherent to the HITCH study [24] may explain the difference in findings. First, that study was an observational cohort; hence, participants who opted to receive the HPV vaccine may have differed from those who did not in other ways that contributed to lower HPV transmission. Second, receipt of the first vaccine dose preceded the start of the partnership for a minimum of 35 of the 63 vaccinated participants in the HITCH study [24], while in the TRAP-HPV study, the start of the relationship preceded vaccination [25]. Finally, the median age at self-reported vaccination in the HITCH study was 18 years [24], whereas in the current study, the median age for receiving the first vaccine dose (equivalent to the median age of participants) was 25.5 years. Thus, participants in the current study may have been exposed to more HPV types prior to receiving the vaccine.

In another analysis of the HITCH cohort, Malagón and colleagues estimated that 43 % of putative incident infections could be latent infections becoming detectable again [36]. The TRAP-HPV study included older participants compared to females in HITCH [36]. Hence, the proportion of detections attributable to re-emerging latent infections could be even greater in the TRAP-HPV study. Although 17.9 % of participants in the current study tested positive for one or more vaccine-targeted HPV types at baseline, given the participants' age, it is likely that many others had been previously exposed to these types and may have carried latent infections. Redetection of latent infections is likely not preventable through vaccination and, thus, would be equally likely to occur in all study arms, which could partially explain the lack of observed protection from recent vaccination.

Another factor that may contribute to the lack of observed protection in the current analysis is the age of participants (mean 25.5 years). A 2020 US study in females 20–29 years of age found that the prevalence of quadrivalent vaccine-targeted HPVs was reduced in those vaccinated with 1, 2, or 3 doses compared to unvaccinated females [37]. However, the reduction in prevalence compared to unvaccinated females was much greater for those vaccinated by age 18 than for those vaccinated after [37]. Furthermore, a systematic review of the effectiveness of HPV vaccination found that studies reporting HPV infection as the endpoint consistently showed lower effectiveness with increasing age at

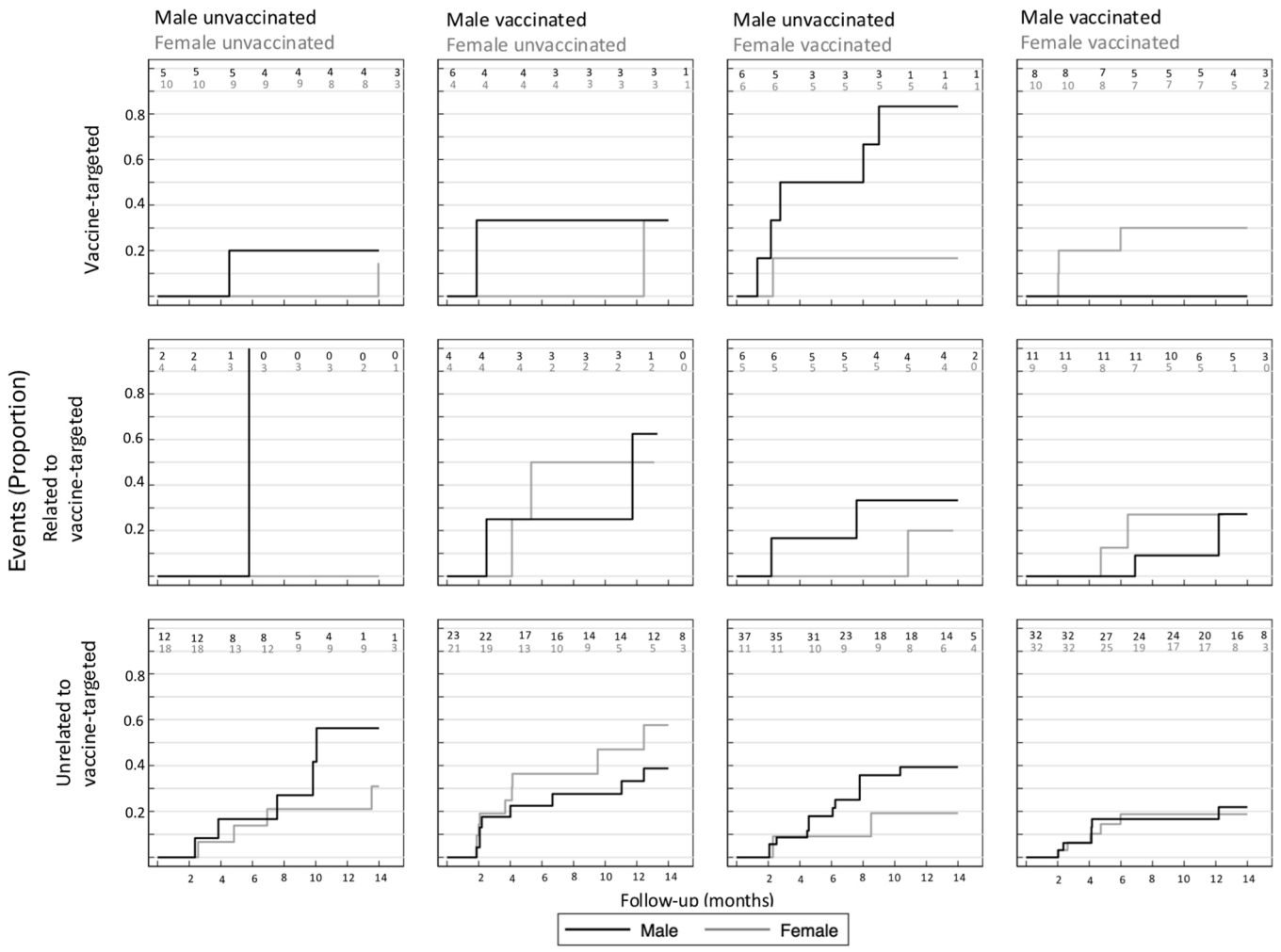

Fig. 3. Transmission of vaccine-targeted HPV types as well as that of HPV types phylogenetically related and unrelated to vaccine-targeted HPV types from females-to-males and from males-to-females among the four vaccination assignment groups. Number of type-specific infections at risk is shown at the top of each graph for female-to-male transmission (black) and male-to-female transmission (grey). Each participant contributes up to 36 HPV types in total: 9 types for vaccine-targeted infections, 7 types for phylogenetically related, and 20 types for phylogenetically unrelated. These analyses were conducted at the HPV-level, meaning that risk-tables reflect the number or type-specific infections which could occur within each HPV category.

vaccination [38]. For example, a 2017 study from Scotland found that while the bivalent vaccine was 89.1 % effective if given between the ages of 12 and 13, it was only 28.9 % effective if given after the age of 18 [39].

Our results suggest that catch-up vaccination for males may offer protection at older ages, as recent HPV vaccination was associated (albeit non-significantly) with lower HPV incidence. However, given the lack of observed protection in female participants, our findings suggest that jurisdictions considering catch-up vaccination should prioritise relatively younger age groups for gender-neutral vaccination, ensuring that individuals are vaccinated before or shortly after sexual debut. Furthermore, our findings highlight the importance of ongoing, regular cervical cancer screening for females who were vaccinated against HPV after sexual debut and suggest that HPV vaccination of adult females (after coitarche) may not substantially reduce cervical cancer incidence.

Several limitations to the current study and analyses need to be acknowledged. First, loss to follow-up was 31.5 % overall, likely due in part to the couple-based nature of the study, as couples were censored from the study if they broke up. However, given that only couples in new relationships were eligible and the follow-up of one year was twice as long as the maximum pre-enrollment relationship duration, it is not surprising that many couples terminated their relationship during the study. Second, although couples were asked not to engage in sexual activity for 48 h prior to clinic visits, some detections could be due to residual depositions of biological material from one's partner rather than actual incident infections [40]. As thiswould be equally likely to occur in any of the trial arms, it could have obscured any underlying pattern. Third, because of the relatively small sample size, few events were observed in each study arm, making it difficult to detect an effect. Based on an estimated effect size of 40 %, we had initially calculated that 90 % power to detect an effect would require 125 couples per study arm and planned to recruit 500 couples [25]. However, given the necessarily stringent recruitment criteria regarding relationship status, duration, and stability, the recruitment of eligible couples proved challenging. The COVID-19 pandemic also exacerbated pre-existing recruitment challenges. Thus, to maintain the scientific value and timeliness of the results, the decision was made to close the study prior to reaching the target sample size.

The above limitations notwithstanding, a unique strength of the TRAP-HPV study is that participants are couples in relatively new sexual relationships, when transmission is most likely. Moreover, the innovative 2 × 2 factorial design allows comparisons by biological sex and vaccination status of both self and partner. Furthermore, since participants were randomized, there is a reasonable assumption of exchangeability between the study arms. Additionally, the prospective nature of the study and frequent follow-up visits allow for a good level of precision

regarding time to events. Importantly, vaccination was administered as part of the study, reducing the chance of misclassification, which is expected with self-reported vaccination status. Finally, the use of type-specific HPV-level infections as the unit of analysis allowed for more insight into transmission dynamics between couples since only the negative partner in a type-specific discordant partnership was at risk of transmission. Type-specific HPV-level infections also provide greater statistical power to detect an effect since each participant contributed time at risk for multiple HPV types.

In conclusion, in this study of sexually active adults with a mean age of 25 years and a median of 6 lifetime vaginal sexual partners, we did not find conclusive evidence of a protective effect from recent HPV vaccination against either incident infection or transmission for oneself or one's partner. Given the low number of events in each study arm and the well-established efficacy of HPV vaccination in preventing HPV infection, these findings should be interpreted with great caution and should not be generalized to younger or less sexually experienced populations. Future studies with larger sample sizes could yield further insights into the effects of HPV vaccination in sexually active adult populations.

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Meeting(s) where the information has previously been presented

Portions of this manuscript's results have been previously presented at a McGill University Division of Cancer Epidemiology monthly seminar on March 5, 2024, Montreal, Canada; EUROGIN 2024: International Multidisciplinary HPV Congress, March 13–16, 2024, Stockholm, Sweden; the Gerald Bronfman Department of Oncology 3rd annual Celebration of Research and Training in Oncology (CORTO) on May 14, 2024, Montreal, Canada; the 2nd Epidemiology Symposium presented by students of l'ESPUM (École de santé publique de l'Université de Montréal) on May 21, 2024, Montreal, Canada; and the IPVC 2024 conference, November 12–15, 2024, Edinburgh, UK.

Author contributions

ELF and ANB conceived the study design. ELF and MZ planned and supervised the study. MZ oversaw data collection and management. AM carried out analyses and drafted the manuscript with support from MZ and ELF. FC supervised HPV genotyping. PPT supervised the study nurses and advised on participant recruitment and sexual health. All authors reviewed, provided critical feedback, and approved the final version of the manuscript.

CRediT authorship contribution statement

Eduardo L. Franco: Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization. **Mariam El-Zein:** Writing – review & editing, Supervision, Project administration, Data curation. **Alissa Moore:** Writing – original draft, Formal analysis. **Ann N. Burchell:** Writing – review & editing, Conceptualization. **François Coutlée:** Writing – review & editing, Resources, Methodology. **Pierre-Paul Tellier:** Writing – review & editing, Project administration.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Eduardo L. Franco reports financial support was provided by Canadian Institutes of Health Research. Eduardo L. Franco reports financial support was provided by Merck Canada Inc. Francois Coutlee reports financial support was provided by Quebec Health Research Fund. Eduardo L. Franco reports a relationship with Merck Canada Inc that includes: consulting or advisory and funding grants. Eduardo L. Franco reports a relationship with Roche that includes: consulting or advisory, funding grants, and non-financial support. Eduardo L. Franco reports a relationship with GSK that includes: consulting or advisory. Francois Coutlee reports a relationship with Merck Sharp & Dohme Corp that includes: funding grants and non-financial support. Francois Coutlee reports a relationship with Becton Dickinson and Company that includes: funding grants and non-financial support. Francois Coutlee reports a relationship with Roche that includes: funding grants, non-financial support, and speaking and lecture fees. Francois Coutlee reports a relationship with Merck that includes: speaking and lecture fees. Eduardo L. Franco has patent related to the discovery "DNA methylation markers for early detection of cervical cancer" pending to Moshe Szyf, David Cheishvili, Mariam El-Zein, and Eduardo L. Franco. Mariam El-Zein has patent related to the discovery "DNA methylation markers for early detection of cervical cancer" pending to Moshe Szyf, David Cheishvili, Mariam El-Zein, and Eduardo L. Franco.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jcv.2025.105779.

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