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Transmission reduction and prevention with HPV vaccination (TRAP-HPV) study protocol: a randomised controlled trial of the efficacy of HPV vaccination in preventing transmission of HPV infection in heterosexual couples

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ABSTRACT

Introduction Human papillomavirus (HPV) is a causal agent of malignancies including cervical, vulvar, vaginal, penile, anal and oropharyngeal cancer, as well as benign conditions such as anogenital warts. HPV vaccination protects individuals against infections with the target HPV types and their clinical outcomes. However, little is known about the protection an immunised individual confers to their sexual partner or its impact on HPV transmission dynamics. In this context, the Transmission Reduction and Prevention with HPV vaccination (TRAP-HPV) study was designed to determine the efficacy of an HPV vaccine in reducing transmission of genital and oral HPV infection in sexual partners of vaccinated individuals.

Methods and analysis The TRAP-HPV study is an ongoing randomised controlled trial among heterosexual couples living in Montreal, Canada. Sexually active couples, aged between 18 and 45 years, who have been in a relationship no longer than 6 months are considered eligible. Participants are independently randomised to receive either the intervention HPV vaccine, Gardasil 9, or a placebo hepatitis A vaccine, Avaxim, creating four vaccination groups among couples: intervention–intervention, intervention–placebo, placebo–intervention and the placebo–placebo. Participants provide genital (vaginal/penile) and oral samples at baseline and five follow-up visits over a 1-year duration. Linear Array HPV genotyping is used to detect 36 HPV types. Cox proportional hazard regression models will be used to estimate the effect of vaccination on HPV transmission.

Ethics and dissemination The TRAP-HPV study received ethical approval by institutional review boards McGill University, Concordia University and Centre Hospitalier de l'Université de Montréal. Before enrolment, all participants provide informed written consent. Results will be published in peer-reviewed journals and presented at national and international conferences. The generated empirical evidence could be used in mathematical models of vaccination to inform policymakers in Canada and elsewhere.

Trial registration number NCT01824537.

Strengths and limitations of this study

- This is the first randomised controlled trial of the efficacy of vaccination to reduce human papillomavirus transmission.
- Individuals within the dyad are randomised independently to the treatment or placebo vaccine, allowing for comparison between four vaccination groups.
- A key logistical challenge in conducting a sexual transmission prevention study is the need for couples to have been recently formed.
- Anal sampling is a deterrent in participant recruitment.

INTRODUCTION

Human papillomavirus (HPV) is the most common sexually transmitted infection and a necessary cause of cervical cancer.[1 2] Epidemiological studies of genital HPV infection are mostly focused on women or men individually, assessing the acquisition of HPV infection and its determinants. However, by excluding the sexual partners, these studies cannot explore the dynamics of HPV transmission within a heterosexual couple. Hence, HPV transmission is best investigated in couple-based studies by examining concordance and discordance of HPV genotypes in partners over time. In such studies, one must include those in recently formed relationships as transmission events would be more likely to occur during the onset of a couple's sexual activity.[3] A couple-based observational study recently provided evidence that HPV vaccination received by women confers some protection against HPV infection to their unvaccinated male sexual partners.[4] To the

best of our knowledge, no randomised controlled trials (RCTs) have studied the impact of vaccination on transmission dynamics within a couple-based study.

Three prophylactic HPV vaccines (cervarix, a bivalent vaccine (types 16 and 18) by GlaxoSmithKline; Gardasil, a quadrivalent vaccine (types 6, 11, 16 and 18) and Gardasil 9, a nonavalent vaccine (types 6, 11, 16, 18, 31, 33, 45, 52 and 58), both by Merck) have been proven in individual-based RCT to be highly effective in preventing infection with the targeted HPV types and associated cervical precancerous lesions.[5–7] Indisputably, HPV vaccination has shifted the paradigm of prevention measures and is expected to have a major impact in reducing the burden of cervical cancer and other HPV-associated malignancies, such as vulvar, vaginal, penile, anal and oropharyngeal cancers, as well as benign conditions, such as anogenital warts and respiratory papillomatosis.[8–10] However, much remains to be understood regarding the effects of HPV vaccination in preventing transmission of target HPV types to sexual partners of vaccinated individuals and its impact on herd immunity.

The objective of the Transmission Reduction and Prevention with HPV vaccination (TRAP-HPV) study is to determine the efficacy of an HPV vaccine in reducing transmission of genital and oral HPV infection in sexual partners of vaccinated individuals. TRAP-HPV will also assess whether a previously infected individual, once vaccinated, is less infective to her or his sexual partner.

METHODS AND ANALYSIS

Study design

The TRAP-HPV study is a randomised, placebo-controlled, double-blinded trial being conducted in Montreal, Canada. This protocol follows the Standard Protocol Items: Recommendations for Intervention Trials checklist of recommended items to address in a clinical trial protocol.[11] The study received ethical approval by institutional review boards at McGill University (A04-M37-12A), Concordia University (30001405), and Centre Hospitalier de l'Université de Montréal (2014–2019, CE 13.016). Amendments to the protocol are approved by the previously mentioned review boards. The protocol was last revised on 12 June 2018 (10th revised version). Before taking part in this exploratory clinical trial, all participants provide informed written consent to the research nurse (online supplementary appendix 1–3 for women, men and the addendum for active study participants during the COVID-19 pandemic, respectively).

Study setting and participant recruitment

Participant's enrolment started in January 2014, and is ongoing. Our study coordinator enrols participants. Initially, participants attended one of two venues for their clinic visit, which provide medical care year-round to students: the McGill University Health Services Clinic or Concordia University Health Services Clinic. At present, starting in September 2018, all participants are seen at the Division of Cancer Epidemiology's research clinic at the Gerald Bronfman Department of Oncology, McGill University.

Recruitment is bolstered through campus-wide appeals, including posters, emails to student lists, promotional videos, online-classified advertising services and word-of-mouth advertising. Additional efforts include mail-outs to students living in residence, classroom presentations in professional schools and information booths at student activities where promotional products are distributed (ie, brochures, promo-button pins and keychains). In July 2017, we implemented a new strategy to boost enrolment. Traditionally, study coordinator(s) would ask potential participants a set of questions to determine their eligibility during the enrolment or screening phase (online supplementary appendix 4). We opted to complement this approach with an online pre-eligibility survey that consists of nine eligibility questions that are answered by potential participants on their own (online supplementary appendix 5). Eligibility is then assessed using a predefined automatically generated algorithm. Potential participants are contacted and informed of their eligibility. This questionnaire is posted on social media, the McGill Cancer Epidemiology website (https://www.mcgill.ca/traphpv/), and online-classified advertising services. To promote participant retention, we send reminder emails to participants before their scheduled study visits and reschedule appointments with participants when they cannot attend their visit.

Eligibility criteria

To be eligible, volunteer couples must (1) not have received the intervention vaccine (Gardasil prior to 8 July 2015 and Gardasil 9 afterwards); (2) plan on remaining in Montreal for at least 1 year; (3) be in a new relationship (onset of sexual activity) that started no more than 6 months prior to study entry; (4) plan on having continued sexual contact with partner; (5) be between 18 and 45 years old; (6) have no history of cervical, penile, oral or anal cancers and (7) be willing to comply with study procedures. Additionally, the female must not be pregnant or plan on immediately becoming pregnant. Concerning criteria 3 and 4, we screen couples based on the Dyadic Adjustment Scale (DAS), a validated instrument to measure the stability of couples' relationships.[12–14] Although the questionnaire is intended for married and common-law couples, participants answer 4 questions (in English or French) applicable to non-cohabitating couples from the Dyadic Satisfaction subscale of the DAS (table 1). These questions gauge the degree of confidence in the partner, likelihood of a separation, and overall satisfaction with the relationship. Couples in which one of the partners scores less than 80% of the maximum score are not enrolled.

Interventions

Once recruited, couples were randomised to one of four treatment or placebo vaccine combinations (table 2) via

Table 1 Questions from the Dyadic satisfaction subscale of the Dyadic Adjustment Scale to determine relationship stability prior to couples enrolment

1) Have you ever considered separation, or terminating your relationship?					
0 Always	1	2	3	4	5 Never
2) In general, would you consider that things are going well between you and your partner?					
0 Always	1	2	3	4	5 Never
3) Do you have trust in your partner?					
0 Always	1	2	3	4	5 Never
4) On a scale of 0–6, describe your degree of happiness as a couple. The degree of happiness found in most relationships would be 3.					
0 Extremely unhappy	1	2	3	4	5 6 Extremely unhappy

a 2-by-2 design where both partners either receive the intervention vaccine or the placebo vaccine, or receive discordant vaccination regimens from the research nurse. Prior to 8 July 2015, Gardasil was used as the intervention vaccine, which allowed for the observation of four infection outcomes (HPVs 6, 11, 16, 18). Henceforth, intervention has been defined as vaccination with Gardasil 9 (Merck).[7] This vaccine allows for the observation of nine HPV outcomes (HPVs 6, 11, 16, 18, 31, 33, 45, 52, 58). The placebo vaccine is the hepatitis A vaccine Avaxim (Sanofi Pasteur). Initially, Havrix (GlaxoSmithKline) was administered as the placebo vaccine until 11 June 2018 (refer to discussion and table 3 for more details regarding intervention and placebo vaccine amendments). Hepatitis A vaccine was chosen as the placebo vaccine because hepatitis A immunisation provides a similar health prevention incentive to study participants as HPV vaccination while preserving the scientific cogency of a 'placebo' comparator. Gardasil 9 requires administration of three doses, while Avaxim only requires 2 doses. Hence, a placebo injection (saline solution) is administered between the hepatitis A vaccination regimen. Accordingly, both treatment and control vaccines have similar regimens, that is, at study entry, 2 months and 6 months.

To ensure that all study participants gain similar health benefits and incentives, and in keeping with ethical values, a crossover of interventions is implemented at the end of the study; the HPV vaccine is offered to all control participants and hepatitis A vaccine to all HPV-immunised participants. The benefit of HPV vaccination would not be significantly delayed for control participants since the study is relatively short (12 months).

Incentives for participation

HPV and hepatitis A vaccines are provided free of charge and participants receive a monetary incentive at every visit. Remuneration per participant is distributed as follows: CAN$120 at enrolment visit; CAN$60 for visits 2, 3 and 4; CAN$80 at visit 5; and CAN$120 at the last visit. In total, individuals are each given CAN$500 (CAN$1000 per couple) as a cash incentive for their participation, if all study visits were to be completed.

Randomisation and blinding

Random allocation of study participants is determined via computer-assisted simple randomisation. Treatment assignment is done via a secure web-based programme at the time the couple is enrolled. Participants, investigators and outcome assessors are blinded to vaccination assignment. Participant blinding is assured because both vaccines (HPV and hepatitis A) and their syringes look identical (previously drawn from blinded vials in a separate room by the nurse) so that participants are unaware of their content. Furthermore, injection pain is expected to be similar for both vaccines. At the end of the study, participants are informed of their allocation.

Data collection procedures

Figure 1 shows the study design, procedures and schedule. Blood samples are collected only at the first visit, whereas oral and penile/vaginal samples are collected at every visit. Anal sampling was discontinued in July 2016 due to its hindering effect on recruitment. Vaginal samples are self-collected at the clinic after participants receive verbal and written instructions from the study nurse. All other samples are collected by trained research nurses. Pending transfer to the laboratory, oral and blood samples are stored in a −20°C freezer while penile and vaginal samples are stored in a 4°C fridge. On arrival to the lab, samples are kept at similar temperature conditions until being processed.

Self-administered web-based questionnaire

Participants complete a self-administered baseline questionnaire at enrolment and a follow-up questionnaire at each of their five subsequent visits (online supplementary

Table 2 Vaccination comparison groups in the TRAP-HPV study 2×2 factorial study design

	Male (M) vaccination	
Female (F) vaccination	**HPV (Gardasil 9) (T)**	**Placebo (Avaxim) (P)**
HPV (Gardasil 9) (T)	M^TF^T	M^PF^T
Placebo (Avaxim) (P)	M^TF^P	M^PF^P

M and F correspond to male and female, respectively. Treatment (T) vaccine switch from Gardasil to Gardasil 9 as of 8 July 2015. Placebo (P) vaccine switch from Havrix to Avaxim as of 4 June 2018.
TRAP-HPV, Transmission reduction and prevention with human papillomavirus.

Table 3 Protocol amendments in chronological order, approved by McGill University's Research Ethics Board

Amendment	Rationale	Date approved
Increase recruitment age from 18 to 26 years to 18–40 years	The vaccine has been shown to be safe and efficacious in older females and males.[49] Based on this, increasing the age range for eligible couples would be safe and will further improve our potential for recruitment.	April 14 to 2014
Increase maximum duration of a relationship from 3 to 6 months	Although the likelihood of HPV transmission to have occurred becomes greater with longer duration of a relationship, evidence from a couple's study conducted by our division, the HPV Infection and Transmission among Couples through Heterosexual activity (HITCH) study, indicated that new HPV infections are still very common among young couples reporting being involved in a sexual relationship for up to 6 months.[29]	April 30 to 2014
Increase compensation from 350 Canadian Dollars (CAD) to 500 CAD per couple	This protocol change was made to improve recruitment.	February 9 to 2015
Switch intervention vaccine from Gardasil to Gardasil 9	The Gardasil 9 amendment was implemented to enhance the health benefit of the study to participants while making this protocol truly cutting edge with respect to the state of HPV science. Consequently, our eligibility criteria regarding prior HPV vaccination status changed from 'must not have been vaccinated with Gardasil' to "must not have been vaccinated with Gardasil 9'.	July 08 to 2015
Increase recruitment age from 18 to 40 years to 18–45 years	An increase in the age range for eligible couples is considered safe and will further improve our potential for recruitment.	February 16 to 2016
Discontinue anal sampling	Potential and recruited participants have confirmed our suspicions that troubling recruitment rates were partially due to the embarrassing and uncomfortable nature of this procedure.	July 14 to 2016
Increase Compensation from 500 CAD to 1000 CAD per couple	In an effort to improve recruitment, remuneration of couples was doubled from CAN$500 to CAN$1000, if all study visits were to be completed.	May 8 to 2017
Switch placebo vaccine from Havrix to Avaxim	The placebo vaccine Aviatrix, a hepatitis A vaccine, has been purchased from GSK. Due to the increased cost of Havrix, we switched to Avaxim by Sanofi Pasteur, also a hepatitis A vaccine. Avaxim is administered to participants using the same blinded and concealed regimen as described in the original protocol. Avaxim and Havrix have been in long-term use in Canada.	June 4 to 2018
COVID-19 Procedural Changes	The following personal protective equipment is used by the research nurse: goggled face shield, disposable gown with long sleeves and elastic in the fists cuffs, sterile gloves, and surgical mask. Participants use the provided face mask and sterile gloves. Participants use alcohol-based hand sanitiser when entering the building and washing/disinfecting hands in the research clinic. The keyboard and other common areas are sanitised after each use. Safe distancing is maintained (keeping a distance of 2 m, except for vaccine administration and collection of biological samples by the research nurse). Appointments are scheduled at sufficiently-spaced time intervals to minimise the number of participants arriving at the study site. The participant informed e-consent form has been updated accordingly.	May 26 to 2020

HPV, human papillomavirus.

appendix 6 and 7 for women, respectively; online supplementary appendix 8 and 9 for men, respectively). At enrolment, participants are introduced to the web-based system and then individually complete their enrolment questionnaire in private. We use a secure, confidential study-designated internet site to provide participants with protected access to the web-based questionnaires by assigned login names and passwords.

Collection of blood specimens

The study nurse collects the blood specimen at baseline according to the Protocol for Collection of Blood Specimens (online supplementary appendix 10). Merck Research Laboratory at Merck's headquarters in Pennsylvania, USA, will conduct competitive Luminex immunoassay with the serum samples to detect and quantify any neutralising antibody response to HPV infection.[15 16]

Collection of oral specimens

The nurse collects a sample of exfoliated cells from representative sites in the oral cavity using a toothbrush and mouthwash according to the Protocol for Collection of Specimens of Exfoliated Cells from the Mouth (online supplementary appendix 11).[17] Samples are centrifuged and the pellet is processed as described below for DNA extraction.

Collection of vaginal specimens

Women are asked to abstain from intercourse a minimum of 48 hours before specimen collection to minimise the risk of contamination with residual male epithelial cells, urethral secretions and/or semen.[18] The instructions for self-collection of vaginal specimens follow those of the validated protocol of Gravitt *et al* (online supplementary appendix 12).[19] The swab is placed directly into

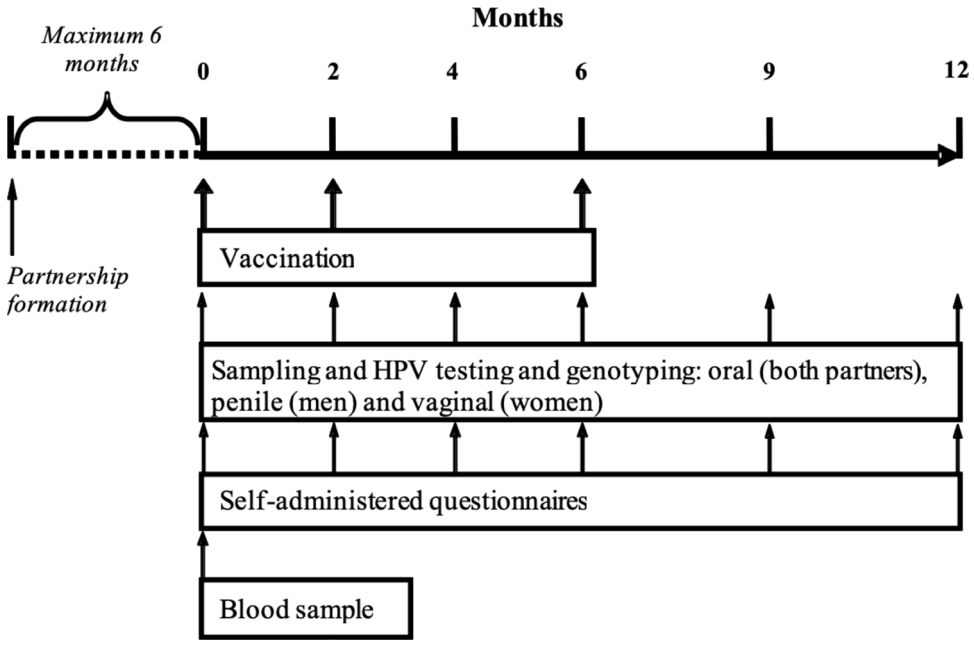

Figure 1 Study design and time points of data collection. Participants in a relationship no longer than 6 months are enrolled in the study. The assigned vaccination regimen is administered at the 0, 2 and 6 months marks. oral, penile, penile (men) and vaginal (women) samples are collected from participants at every study visit. Blood samples are collected from participants only at enrolment. HPV, human papillomavirus.

the plastic vial with the PreservCyt transport medium (ThinPrep PreserveCyt Solution, Hologic, Marlborough, Mass.), which adequately preserves exfoliated specimens for DNA, RNA and protein analyses. Self-collected vaginal samples have been shown to be valid for research and clinical purposes, and acceptable to women.[19 20]

Collection of penile skin swabs

Men are asked to abstain from sexual intercourse for 48 hours preceding collection to reduce the possibility of detecting HPV carriage from residual female secretions.[21] The research nurse conducts an external examination of the genital area to note circumcision status and presence of any relevant clinical findings. The nurse collects the penile sample according to the Protocol for Collection of Specimens of Male Penile Skin Swabs (online supplementary appendix 13). The research nurse collects the specimen using emery paper (600A-grit Wetordry Tri-M-ite; 3M) exfoliation, followed by swabbing with a Dacron applicator moistened with sterile normal saline.[22] The nurse uses a new wet swab and sweep 360° around the coronal sulcus and then another 360° around the glans penis. The nurse proceeds to use a new wet swab to sample the entire skin surface of each quadrant of the penile shaft (left and right ventral, and left and right dorsal). Afterwards, each swab is placed into an individual PreservCyt-containing vial and labelled according to the anatomic site. Previous research on penile skin swabbing to detect HPV DNA has proven this method to be reliable.[23]

HPV testing

DNA is extracted from samples using the Master Pure extraction kit (Epicentre, Madison, Wisconsin, USA).[24] HPV genotyping is done using the Linear Array HPV Genotyping Test (Roche Molecular Systems, Indianapolis, Indiana, USA).[25] Using the PGMY09/11 consensus primer system which targets the L1 gene of the HPV genome, this assay can detect 36 types (HPVs 6, 11, 16, 18, 26, 31, 33–35, 39, 40, 42, 44, 45, 51–54, 56, 58, 59, 61, 62, 66–73, 81–84 and 89). Coamplification of β-Globin is performed to assess specimen quality.

Study outcomes

For each anatomic site, the primary outcome will be transmission reduction of HPV infections of target HPV vaccine types (HPVs 6, 11, 16, 18, 31, 33, 45, 52, and 58) over time in Avaxim-administered sexual partners of HPV vaccinated individuals, corresponding to the combinations M^TF^P and M^PF^T (table 2). The control group consists of couples randomised to both participants receiving Avaxim, denoted as the M^PF^P group. The fully protected group is represented by the combination M^TF^T. We will also measure prevalence and incidence of HPV types covered by the intervention vaccine in all collected samples, for each visit and among all participants.

Reduction in HPV type concordance (for the nine target types) will be evaluated over time between vaccination groups. These comparisons will be done with due attention to the enrolment HPV type-specific infection status of participants. For instance, we expect that an Avaxim-treated woman who is positive for HPV6 in the oral specimen, but negative for this type in the vaginal specimen, may derive benefit if her partner had received the intervention vaccine, even if he is HPV6 positive in the penile sample. We assume that protection via vaccination

is pan-mucosal, via transudation of neutralising antibodies and may mediate transmission.

Data management

Data management and project coordination is done at the McGill's Division of Cancer Epidemiology coordination centre. Study oversight and data management are led by the study director (ME-Z) and principal investigator (ELF). The research staff have access to the secure study-designated website containing participant and study visit information. Along with laboratory results, all participant information is confidential and stored in a secure location. All participant data are checked monthly for quality assurance.

Sample size

There are no published empirical estimates of the expected level of transmission reduction. Our informal consultation with experts in the field indicated that 40% reduction in transmission would be a conservative estimate; it would represent the expected magnitude of a protective effect in the discordant vaccination groups where the partner receiving a placebo is the one to be protected. Using the Bernstein and Lagakos approach,[26] we determined that a total of 500 couples (125 couples per group/cell in table 2) are required for 90% power, with type 1 error of 0.05, and one-sided hypothesis for a 40% reduction in transmission rate, assuming a cumulative 16% lost to follow-up at month 12 (attrition rate of 2.7% per-visit). Empirically based estimates of parameters for sample size calculation were obtained from our unit's molecular epidemiological investigations of the HITCH cohort study.[27–29] We also assumed gender equivalent rates of transmission as per findings in the HITCH study.[29]

Statistical methods

We hypothesise that HPV vaccination would be effective in reducing the risk of HPV transmission to sexual partners. The study design offers the opportunity to measure transmission events in multiple mucosal sites for multiple HPV types, over multiple clinic visits, and for both directionalities (ie, male to female and female to male). We will take advantage of advanced regression methods as a framework for measuring the effects expected via HPV vaccination.

In the simplest core formulation (eg, analysing a single HPV type and a single mucosal site), we will use the Kaplan-Meier technique to plot the cumulative probability of HPV infection in sexual partners of vaccinated versus unvaccinated individuals against follow-up time. Using the layout in table 2, this implies comparing HPV infection histories of women in the $M^{T}F^{P}$ and $M^{P}F^{P}$ groups and men in the $M^{P}F^{T}$ and $M^{P}F^{P}$ groups. Expectedly, protection is also likely to occur via cumulative effects observable via HPV detection in multiple mucosal sites; we will address this by conducting time to event analysis.

We will use the log-rank test for statistical comparisons in HPV transmission between vaccine and control groups. Cox proportional hazard regression models will be used to estimate the effect of vaccination on HPV transmission to sexual partners based on HRs and their respective 95% CIs. Time to HPV infection in days will be defined as the time from study enrolment to infection date. In addition to the intention-to-treat analysis approach, we will perform regression models to examine the role of several candidate determinants in mediating transmission and protective effects.

Furthermore, cumulative risk models will be fitted with type-specific transmission as an outcome. Generalised estimating equations (GEE) models will be used to incorporate data across multiple HPV types,[30] to account for repeated HPV prevalence data across types and study visits involving the same participant. In a single GEE logistic regression model, we will consider type-specific infection events for each vaccine HPV type as separate transmission endpoints and then estimate the exposure effect on selected HPVs as a group, as we have published.[27 28] Mixed-effects models will also be fitted incorporating repeated HPV transmission data across HPV types and visits involving the same participant.[31] Couples who break-up and end their relationship before their last visit will be censored of the study. Since vaccination protection is expected to begin as early as the first dose, we can expect to analyse reductions in transmission with a subset of visits for a few couples before the full set of visits is completed, which will allow for an interim analysis to be conducted before study termination.

Data monitoring and adverse events

An independent data safety monitoring board will review the interim analysis results. The analysis is planned for when we have recruited half of the target sample size (250 couples) or when 100 couples complete all six visits. We will use all available data when either condition occurs first. We will seek advice from McGill University's Research Ethics Board concerning the composition of this board; members will likely be nominated outside of our purview. The type 1 error for concluding efficacy will be controlled by the Lan-Demets spending function[32] with O'Brien and Fleming type boundaries.[33]

Patient and public involvement

Prior to commencement of the TRAP-HPV study, we conducted a qualitative assessment to explore the acceptability of proposed study procedures and invite recommendations on ways to improve them. We held a focus group with 13 heterosexual couples within the eligible age range of the TRAP-HPV study to resemble potential participants. Focus group participants attended a presentation of the proposed trial procedures then engaged in discussions regarding potential concerns and improvements. Topics discussed related to inclusion criteria, censoring due to break-up, lost of

follow-up, ethical considerations regarding the placebo and attractiveness of the study to similar couples. Results from the focus group inform our trial procedures.

Dissemination policy

Information gained from this study will be published in peer-reviewed journals and presented at national and international conferences. In the context of knowledge translation, the generated empirical evidence could be used in mathematical models of vaccination to inform policymakers in Canada and elsewhere. The implications for mathematical models is discussed further in the discussion.

Preliminary recruitment findings

As of April 2020, we have enrolled 167 couples since recruitment commenced in January 2014. Our records show that 81 couples have been recruited via posters, 47 via online-classified ads (Kijiji, McGill Classified ads and Facebook), 18 couples via word of mouth, and one via a study promotion during a university orientation event, while 12 couples did not specify the recruitment method. So far, 71 couples have completed all six visits, 62 couples withdrew before their last visit and 31 couples with ongoing participation.

DISCUSSION

Logistical issues have been the main challenge for the slow accrual rates. We have since made some changes to the eligibility criteria to improve enrolment while simultaneously conserving the integrity of the study design. The greatest hindrance was the initial short-latency requirement of a new relationship. After the first two couples were enrolled, the maximum relationship duration of 3 months was increased to 6 months. Other efforts to improve recruitment rates involved increasing the upper age limit for participants from 26 to 40 years of age after two couples were recruited and increasing it once more for an upper age limit of 45 years old after enrolling 31 couples. In addition, compensation was increased twice. After recruiting 15 couples, it was increased from CAN$350 to CAN$500 per couple and further increased to CAN$1000 after 68 couples were recruited. Because our recruiters refer to conversations with candidate participants in which they disclose feelings of embarrassment, pain or discomfort in undergoing anal sampling, as deterrents to their participation in TRAP-HPV, the decision was made to discontinue the collection of anal samples after 48 couples were recruited.

Three other protocol amendments have been implemented, unrelated to increasing enrolment rates. After recruiting 23 couples, Gardasil was replaced with Gardasil 9 as the intervention vaccine to increase the study's efficiency in measuring the outcome and to confer increased health benefits to participants. The other protocol amendment was the placebo vaccine substitution, from Havrix (GlaxoSmithKline) to Avaxim (Sanofi Pasteur) after 114 couples were recruited due to increased price of the former. Study enrolment and clinic visits were put on hold on 13 March 2020, following the university lockdown due to the COVID-19 pandemic. On 26 May 2020, we received approval from the university to resume clinic visits for participants with impending vaccination visits. We have put a number of safety measures in place to optimise the safety of participants and our research nurse, such as the use of personal protective equipment, distancing while in the research clinic, scheduling appointments at sufficiently spaced time intervals, and sanitising keyboards and other common areas after each use. For a more detailed list of amendments, refer to table 3.

To our knowledge, this is the first RCT to investigate HPV transmission reduction via vaccination within couples. Additionally, the balanced randomised population of men and women may help shed light into whether biological sex-specific differences exist concerning the efficacy of HPV vaccination. Few previous studies[34–38] have explored HPV transmission between sexually active partners, among which only two couple-based studies have recruited ~500 couples,[39 40] similar to our target sample size. One distinct feature of our study is the implementation of HPV vaccination to a couple-based transmission study. In general, vaccination programmes aim to be cost-effective by reaching sufficiently high coverage to reduce transmission to levels that are low enough to permit additional protection to susceptible, unvaccinated individuals; a concept broadly designated as herd immunity. Given the long timescales involved, mathematical models have played an important role in predicting herd immunity thresholds and informing policy decisions regarding HPV vaccination strategies. Indeed, health economic models on the impact of HPV vaccination have shown the cost-effectiveness of HPV vaccination in 12-year-old North American girls compared with screening.[41–44] The added benefits of vaccinating boys have been also evaluated, with mixed results.[45 46] We concluded that potential incremental gains of vaccinating boys may be limited by the predicted herd immunity impact of vaccinating girls under moderate to high vaccine coverage.[47] However, differences in model structure and assumptions have made it difficult to compare findings across studies and apply them to policy evaluations. A key source of heterogeneity in health economic studies of the impact of HPV vaccination relates to HPV transmission dynamics.[48] Since no vaccination study has examined the dynamics of HPV transmission, the TRAP-HPV study would provide relevant empirically derived estimates for health economic models. These estimates would confirm whether a universal vaccination strategy is appropriate in settings that have adopted such a strategy and if it should be implemented in places where the HPV vaccination strategy is focused solely on individuals assigned female at birth.

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Contributors ELF and AB conceived and designed the trial. ELF and ME-Z supervise the study. AM and ME-Z are responsible for data management. AM drafted the manuscript under the supervision of ME-Z and ELF. FC supervises HPV testing and genotyping, and provided several methodological contributions. P-PT supervises the study nurses and advises the study team concerning issues related to participant recruitment and sexual health. All authors revised the manuscript and approved the final draft.

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Competing interests ELF reports grants and personal fees from Merck, grants, personal fees and non-financial support from Roche, and personal fees from GSK, outside the submitted work. FC has received grants or free reagents through his institution from Merck Sharp and Dome, Becton Dickinson and Roche, as well as honoraria from Merck and Roche for lectures on HPV.

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REFERENCES

1 International Agency for Research on Cancer. Human papillomaviruses. *IARC Monogr. Eval. Carcinog. risks to humans* 2007;90:468–71.
2 Walboomers JM, Jacobs MV, Manos MM, *et al*. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999;189:12–19.
3 Burchell AN, Winer RL, de Sanjosé S, *et al*. Chapter 6: epidemiology and transmission dynamics of genital HPV infection. *Vaccine* 2006;24 Suppl 3:S52–61.
4 Wissing MD, Burchell AN, El-Zein M, *et al*. Vaccination of young women decreases human papillomavirus transmission in heterosexual couples: findings from the Hitch cohort study. *Cancer Epidemiol Biomarkers Prev* 2019;28:1825–34.
5 Harper DM, Franco EL, Wheeler C, *et al*. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet* 2004;364:1757–65.
6 Garland SM, Hernandez-Avila M, Wheeler CM, *et al*. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N Engl J Med* 2007;356:1928–43.
7 Joura EA, Giuliano AR, Iversen O-E, *et al*. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. *N Engl J Med* 2015;372:711–23.
8 Monk BJ, Tewari KS. The spectrum and clinical sequelae of human papillomavirus infection. *Gynecol Oncol* 2007;107:S6–13.
9 Muñoz N, Bosch FX, de Sanjosé S, *et al*. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med* 2003;348:518–27.
10 Schiffman M, Castle PE, Jeronimo J, *et al*. Human papillomavirus and cervical cancer. *Lancet* 2007;370:890–907.
11 Chan AW, Tetzlaff JM, Altman DG, *et al*. Spirit 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;13:1501–7.
12 Spanier GB. Measuring Dyadic adjustment: new scales for assessing the quality of marriage and similar dyads. *J Marriage Fam* 1976;38:15–28.
13 Graham JM, Liu YJ, Jeziorski JL. The Dyadic adjustment scale: a reliability generalization meta-analysis. *J Marriage Fam* 2006;68:701–17.
14 Baillargeon J, Dubois G, Marineau R. Traduction française de l'Échelle d'ajustement dyadique [French translation of the Dyadic Adjustment Scale]. *Rev Can des Sci du Comport* 1986;18:25–35.
15 Dias D, Van Doren J, Schlottmann S, *et al*. Optimization and validation of a multiplexed Luminex assay to quantify antibodies to neutralizing epitopes on human papillomaviruses 6, 11, 16, and 18. *CVI* 2005;12:959–69.
16 Opalka D, Lachman CE, MacMullen SA, *et al*. Simultaneous quantitation of antibodies to neutralizing epitopes on virus-like particles for human papillomavirus types 6, 11, 16, and 18 by a multiplexed Luminex assay. *Clin Diagn Lab Immunol* 2003;10:108–15.
17 Herrero R, Castellsagué X, Pawlita M, *et al*. Human papillomavirus and oral cancer: the International agency for research on cancer multicenter study. *J Natl Cancer Inst* 2003;95:1772–83.
18 Macaluso M, Lawson ML, Hortin G, *et al*. Efficacy of the female condom as a barrier to semen during intercourse. *Am J Epidemiol* 2003;157:289–97.
19 Gravitt PE, Lacey JV, Brinton LA, *et al*. Evaluation of self-collected cervicovaginal cell samples for human papillomavirus testing by polymerase chain reaction. *Cancer Epidemiol Biomarkers Prev* 2001;10:95–100.
20 Wright TC, Denny L, Kuhn L, *et al*. Hpv DNA testing of self-collected vaginal samples compared with cytologic screening to detect cervical cancer. *JAMA* 2000;283:81–6.
21 Bleeker MCG, Hogewoning CJA, Van Den Brule AJC, *et al*. Penile lesions and human papillomavirus in male sexual partners of women with cervical intraepithelial neoplasia. *J Am Acad Dermatol* 2002;47:351–7.
22 Weaver BA, Feng Q, Holmes KK, *et al*. Evaluation of genital sites and sampling techniques for detection of human papillomavirus DNA in men. *J Infect Dis* 2004;189:677–85.
23 Baldwin SB, Wallace DR, Papenfuss MR, *et al*. Human papillomavirus infection in men attending a sexually transmitted disease clinic. *J Infect Dis* 2003;187:1064–70.
24 Habis AH, Vernon SD, Lee DR, *et al*. Molecular quality of exfoliated cervical cells: implications for molecular epidemiology and biomarker discovery. *Cancer Epidemiol Biomarkers Prev* 2004;13:492–6.
25 Coutlée F, Rouleau D, Petignat P, *et al*. Enhanced detection and typing of human papillomavirus (HPV) DNA in anogenital samples with PGMY primers and the linear array HPV genotyping test. *J Clin Microbiol* 2006;44:1998–2006.
26 Bernstein D, Lagakos SW. Sample size and power determination for stratified clinical trials. *J Stat Comput Simul* 1978;8:65–73.
27 Burchell AN, Tellier P-P, Hanley J, *et al*. Influence of partner's infection status on prevalent human papillomavirus among persons with a new sex partner. *Sex Transm Dis* 2010;37:34–40.

28 Burchell AN, Tellier P-P, Hanley J, *et al*. Human papillomavirus infections among couples in new sexual relationships. *Epidemiology* 2010;21:31–7.
29 Burchell AN, Coutlée F, Tellier P-P, *et al*. Genital transmission of human papillomavirus in recently formed heterosexual couples. *J Infect Dis* 2011;204:1723–9.
30 LIANG K-YEE, ZEGER SL. Longitudinal data analysis using generalized linear models. *Biometrika* 1986;73:13–22.
31 Xue X, Gange SJ, Zhong Y, *et al*. Marginal and mixed-effects models in the analysis of human papillomavirus natural history data. *Cancer Epidemiol Biomarkers Prev* 2010;19:159–69.
32 Lan KK, Rosenberger WF, Lachin JM. Use of spending functions for occasional or continuous monitoring of data in clinical trials. *Stat Med* 1993;12:2219–31.
33 O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979;35:549.
34 Widdice L, Ma Y, Jonte J, *et al*. Concordance and transmission of human papillomavirus within heterosexual couples observed over short intervals. *J Infect Dis* 2013;207:1286–94.
35 Mbulawa ZZA, Johnson LF, Marais DJ, *et al*. The impact of human immunodeficiency virus on human papillomavirus transmission in heterosexually active couples. *J Infect* 2013;67:51–8.
36 Hernandez BY, Wilkens LR, Zhu X, *et al*. Transmission of human papillomavirus in heterosexual couples. *Emerg Infect Dis* 2008;14:888–94.
37 Nyitray AG, Lin H-Y, Fulp WJ, *et al*. The role of monogamy and duration of heterosexual relationships in human papillomavirus transmission. *J Infect Dis* 2014;209:1007–15.
38 Su Y, Wei F, Huang X, *et al*. Prevalence, concordance, and transmission of human papillomavirus infection among heterosexual couples in Liuzhou, China: an observational perspective study. *J Infect Dis* 2019;220:980–9.
39 Liu M, He Z, Zhang C, *et al*. Transmission of genital human papillomavirus infection in couples: a population-based cohort study in rural China. *Sci Rep* 2015;5:1–10.
40 El-Zein M, Coutlée F, Tellier P-P, *et al*. Human papillomavirus infection and transmission among couples through heterosexual activity (Hitch) cohort study: protocol describing design, methods, and research goals. *JMIR Res Protoc* 2019;8:e11284.
41 Brisson M, Van de Velde N, De Wals P, *et al*. The potential cost-effectiveness of prophylactic human papillomavirus vaccines in Canada. *Vaccine* 2007;25:5399–408.
42 Goldie SJ, Kohli M, Grima D, *et al*. Projected clinical benefits and cost-effectiveness of a human papillomavirus 16/18 vaccine. *J Natl Cancer Inst* 2004;96:604–15.
43 Hughes JP, Garnett GP, Koutsky L. The theoretical population-level impact of a prophylactic human papilloma virus vaccine. *Epidemiology* 2002;13:631–9.
44 Diaz M, Kim JJ, Albero G, *et al*. Health and economic impact of HPV 16 and 18 vaccination and cervical cancer screening in India. *Br J Cancer* 2008;99:230–8.
45 Elbasha EH, Dasbach EJ, Insinga RP. Model for assessing human papillomavirus vaccination strategies. *Emerg Infect Dis* 2007;13:28–41.
46 Taira AV, Neukermans CP, Sanders GD. Evaluating human papillomavirus vaccination programs. *Emerg Infect Dis* 2004;10:1915–23.
47 Brisson M, van de Velde N, Franco EL, *et al*. Incremental impact of adding boys to current human papillomavirus vaccination programs: role of herd immunity. *J Infect Dis* 2011;204:372–6.
48 Ferko N, Postma M, Gallivan S, *et al*. Evolution of the health economics of cervical cancer vaccination. *Vaccine* 2008;26 Suppl 5:F3–15.
49 Castellsagué X, Muñoz N, Pitisuttithum P, *et al*. End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24-45 years of age. *Br J Cancer* 2011;105:28–37.