Transmission Reduction and Prevention with HPV Vaccination

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Couple-based studies

- HPV transmission investigated in longitudinal couple-based studies

- Recently formed relationships: optimal for examining transmission dynamics

- HITCH: only HPV couple-based transmission study to target recently formed couples
  - Vaccination → transmission reduction (Wissing, Cancer Epidemiol Biomarkers Prev, 2019)

- No RCTs on the reduction of HPV transmission in couple-based studies
Objective: To determine the efficacy of an HPV vaccine in reducing transmission of genital and oral HPV infection to sexually active heterosexual partners of HPV vaccinated individuals.
# 2x2 Factorial Design

<table>
<thead>
<tr>
<th>Female (F) vaccination</th>
<th>Male (M) vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV (Gardasil 9: T)</td>
<td>$M^{TF_T}$</td>
</tr>
<tr>
<td>Placebo (Hepatitis A: P)</td>
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Sample size

- **500 couples needed**

- Based on Bernstein and Lagakos approach *(Bernstein, J Clin Microbiol, 2006)*
  - 90% power
  - type one error: 0.05
  - one-sided hypothesis for reductions: 40% rate of transmission
  - assuming cumulative 16% loss to follow-up at month 12
    - attrition rate: 2.7% per-visit
Eligibility criteria

- Volunteer couples must:
  1. not have been vaccinated with the intervention vaccine.
  2. plan on remaining in Montreal for at least 1 year.
  3. be in a new relationship that started no more than six months prior to study entry.
  4. plan on having continued sexual contact with partner.
  5. be between 18-45 years old.
  6. have no history of cervical, penile, oral or anal cancers.
  7. be willing to comply with study procedures.
Recruitment

- Ongoing since January 2014
- Recruitment strategies:
  - posters
  - e-mails to student lists
  - promotional videos
  - online classified advertising services
  - word-of-mouth
- Untraditional approach: potential participants answer pre-eligibility survey
Time points

Months

0  2  4  6  9  12

- Vaccination
- Oral, penile, and vaginal sampling
- Self-administered questionnaires
- Blood sample

Maximum 6 months

Partnership formation
HPV Testing

- Master Pure extraction kit (Epicenter, Madison, Wisconsin) (Habis, Cancer Epidemiol Biomarkers Prev, 2004)

- Linear Array HPV Genotyping Test (Roche Molecular Systems, Indianapolis, Indiana) (Coutlée, J Clin Microbiol, 2006)
  - Detects 36 HPV types
    - 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
  - PGMY09/11 consensus primer system targets L1 gene
Outcomes

- Reduction of HPV infections with target HPV vaccine types in multiple anatomic sites in Avaxim-administered sexual partners of HPV vaccinated individuals
- Reduction in HPV type concordance, evaluable as per these group contrasts

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Statistical analysis

- Advanced regression methods

- Kaplan-Meier: plot the cumulative probability of HPV infection in sexual partners of vaccinated versus unvaccinated individuals against follow-up time

- Log-rank test: comparisons in HPV transmission between vaccine & control groups

- Additional cumulative risk models fitted with type-specific transmission as an outcome
Strengths

- First RCT to investigate HPV transmission reduction via vaccination within couples

- Few couple-based studies have recruited a target sample size ≥500 couples
  - 502 (El-Zein, JMIIR Res Protoc, 2019)
  - 874 (Liu, Sci Rep, 2015)

- TRAP-HPV could provide empirically-derived estimates for health economic models and mathematical models predicting herd immunity
Challenges & Amendments

- Upper age limit: increased from 26 to 40 years old, and once more to 45 years old
- Compensation: increased from $350 to $500 per couple and further to $1000
- Collection of anal samples discontinued
- Gardasil replaced with Gardasil 9 as intervention vaccine
- Havrix (GlaxoSmithKline) replaced with Avaxim (Sanofi Pasteur) as placebo vaccine
446 assessed for eligibility

- 286 ineligible

160 randomized

- 43 allocated to $M^{TF^T}$
  - 21 completed
  - 12 partial FU
  - 10 ongoing

- 34 allocated to $M^{TF^P}$
  - 13 completed
  - 15 partial FU
  - 6 ongoing

- 40 allocated to $M^{PF^T}$
  - 18 completed
  - 12 partial FU
  - 10 ongoing

- 43 allocated to $M^{PF^P}$
  - 16 completed
  - 20 partial FU
  - 7 ongoing
Acknowledgements

TRAP-HPV study group

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