Prevalence of HPV infection using self-sampling screening and monitoring the Earlier Impact of HPV-Vaccination Program in Switzerland

Study protocol – version 5

08 june 2016

- **Principal Investigator:** Pr Patrick Petignat, MD, University Hospitals of Geneva, Head of Gynecologic Division, CH-1211 Geneva 14, patrick.petignat@hcuge.ch

❖ **Co- investigators:**

Emilien Jeannot, Msc, MPH, PhD cand. Institute of Global Health, Department of Health and Community Medicine, University of Geneva and University of Applied Sciences Western Switzerland, Geneva, Switzerland **Mail :** Emilien.Jeannot@unige.ch

Dr. Pierre Vassilakos, MD, Geneva Foundation for Medical Education and Research, pierrevassilakos@bluewin.ch

Dr. Rosa Catarino MD, University Hospitals of Geneva, Head of Gynecologic Division, CH-1211 Geneva 14, RosaIsabel.PintoCatarino@hcuge.ch.

Dr. Manuela Viviano, University Hospitals of Geneva, Head of Gynecologic Division, CH-1211 Geneva 14, Manuela.Viviano@hcuge.ch

Pr Emmanuel Kalenbele, PhD, Institute of Global Health, Department of Health and Community Medicine, University of Geneva, Emmanuel.Kabengele@unige.ch

Abstract

Background: Currently prevalence of HPV infections for high risk strains among young women in Switzerland is unknown. In addition, since 2008 a vaccination program to prevent these infections has been implemented in a number of cantons, but its actual population impact is currently unknown. For now, HPV screening in Switzerland is mainly performed by gynecologists or during gynecological consultation at hospital. This method is certainly effective, but expensive; population coverage of screening is still insufficient. A whole segment of the target population does not participate in this screening especially young people of foreign origin, for various reasons: economic cost, no gynecological, and for other reasons.

Several studies raise the effectiveness and efficiency of self-sampling to increase coverage of screening, and the rate of participation of non-participants. Through this study, we evaluate the possibility to use self-sampling as a screening tool in a real population, document the effectiveness of this vaccination on the prevalence of HPV infections and assess evolution of infection and clearance of HPV virus during 5 years in a population of young unvaccinated and vaccinated girls.

Method: During the study, each woman will perform a vaginal swab sampling by auto to research HPV. These samples will be sent to a laboratory where HPV typing is done by PCR using the Anyplex ™ II technology.

The study will focus on a sample of 400 young women. Participants must complete a questionnaire containing demographic questions and their HPV immunization status. Vaccination coverage expected in this population is about 50%. Depending on the state of vaccination, two different groups will be vaccinated vs unvaccinated (200 women per group). The cases of HPV infection are then calculated for each group and compared as a function of the status of vaccination. Statistical tests will be applied McNemar's test for comparison between the HPV prevalence rates between the 2 groups.

Expected Results: This study will allow us to confirm the possibility of using self-sampling as a method of screening and monitoring of HPV infections in the general population, it will also enable us to document the effectiveness of HPV vaccination by comparing prevalence rate of HPV infections among a group of young girls vaccinated and not vaccine and assess evolution of infection and clearance of HPV virus.

Key words: cervical cancer, self-sampling, Human papillomavirus (HPV)

1. Background

Human papillomavirus (HPV) vaccination to prevent cervical cancer has been introduced in Switzerland in 2008. Recommendations are that young girls aged 11 to 14 are included in the immunization schedule program at school and girls aged 15 to 19 are included in a "catch-up program", for a transition period, until 2012. Within school-based program, the vaccine uptake has been achieved to date with a 60% course completion, but lower rate (20%) has been observed in cantons having adopted an "opportunistic" vaccination strategy.

Monitoring public health impact is an essential component of the intervention. Since the eventual cervical cancer disease reduction will be only able to be evaluated decades after exposure, current monitoring activity will focus on the anticipated earlier reduction of HPV vaccine-type in the population. In 2015, seven years passed since the first vaccinated cohorts entered the program; "school-vaccinated" women will be of 18 years old and "catch-up vaccination" will be of 32 years old. Prior introduction of the vaccine in Switzerland, the only available data was from HPV testing performed with residual cervical screening sample from women attending cervical cancer screening (1, 2). To date, there is no Swiss available data about the impact of HPV vaccination. The earlier sign of HPV vaccination could probably be observed on the HPV prevalence and precursor lesion in women population. To date, there is no Swiss available data about the impact of HPV vaccination. The earlier sign of HPV vaccination could probably be observed on the HPV prevalence and precursor lesion in women population. An observational study conducted in Australia support that the incidence of genital warts decreases in younger women (3-5). Another trial conducted in England (6) has showed that the national HPV immunization program seemed successful in preventing HPV 16/18 infection in sexually active young women. The prevalence of HPV 16/18 infection in the post-immunization survey was 6.5% amongst 16–18 year olds, compared to 19.1% in the similar survey conducted prior to the introduction of HPV immunization.

In USA, the US population-based sentinel surveillance system to monitor HPV impact show that from 2008 to 2012, prevalence of HPV 16/18 in CIN2+ lesions statistically significantly decreased from 53.6% to 28.4% among women who received at least one dose HPV vaccine (*Ptrend*<.001) but not among unvaccinated women (57.1% vs 52.5%; Ptrend=.08) or women with unknown vaccination status (55.0% vs 50.5%; *Ptrend*=.71) (7). More recently, a systematic review and meta-analysis describe that, in countries with female vaccination coverage of at least 50%, HPV type 16 and 18 infections decreased significantly between the pre-vaccination and post-vaccination periods by 68% (RR 0·32, 95% CI 0·19-0·52) and anogenital warts decreased significantly by 61% (RR 0·39, 0·22-0·71) in girls 13-19 years of

age. Comparing to countries with female vaccination coverage lower than 50%, significant reductions in HPV types 16 and 18 infection (RR 0·50, 95% CI 0·34-0·74]) and in anogenital warts (0·86 [95% CI 0·79-0·94]) occurred in girls younger than 20 years of age, with no indication of cross-protection or herd effects (8).

To evaluate the effectiveness of this vaccination, it is important to detect quickly, economically and efficiently prevalence of HPV high risk in our population. In Switzerland, young women who want to get tested do either with their gynecologists or so via gynecological hospital visits. This method is certainly effective, but expensive, furthermore screening coverage is still insufficient (only 30 to 40 % women's don't participle at the screening) in Switzerland. Also a part of our study population don't participate in screening such young people of foreign origin for various reasons, no gynecological medecin, economic cost etc ...

Several studies raise the effectiveness and efficiency (9) of the self sampling to increase screening coverage (10), participation rate of nonattenders (11, 12) self-sampling has been nearly as sensitive as clinician-obtained cervical samples and more sensitive than cytology for the detection of cervical intraepithelial neoplasia (CIN) for lesions of high-grade CIN-II or higher (CIN-II+) (13-14) .

Through this study we want to evaluate the possibility of using self sampling as a screening tool in a real population, yet a study in Geneva showed the possibility of its use for screening a population not visiting gynecological hospital visits (15), but the actual population use remains to be demonstrated.

2. Objectives

Through this study, we evaluate the possibility to use self sampling as a screening tool in a real population, document the effectiveness of this vaccination on the prevalence of HPV infections and assess evolution of infection and we will assess the evolution of viral infection and clearance of throughout 5 years in a population of young, unvaccinated and vaccinated girls.

Primary objective

- Explored the feasibility of establishing a home-based Self-HPV screening strategy in general population

Secondary objective

- To determine the HPV prevalence of vaccine-type: 19 high-risk HPV types (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 69, 73, 82) and 9 low-risk HPV types(6,

11, 40, 42, 43, 44, 54, 61, 70) in young women population attending High schools in Geneva and Faculty of Medicine at the University of Geneva.

- To generate data about vaccination impact and vaccine coverage.

- To assess the infection's evolution and clearance of HPV throughout 5 years in a population of young, unvaccinated and vaccinated young women

3. Material and method

Inclusion criteria:

- Eligible women aged between 18-31 years attending of Haute Ecole de Santé – Genève and Faculty of Medicine at the University of Geneva.
- Understands study procedures and accepts voluntarily to participate by signing the informed consent form (ICF)

Exclusion criteria:

- History of hysterectomy or treatment on the cervix during the last 12 months.

Study Design and Methods

Setting: The study will be conducted in collaboration with the High school of health in Geneva and Faculty of Medicine at the University of Geneva. The study will be proposed to 400 women attending these schools.

Recruitment: It will take place in the health school of health and Faculty of Medicine at the University of Geneva. Trial information on the University website will be available; it will also contain a phone number for helpline. Cards to check eligibility, registration and scheduling will be available. The HPV self-collection kit will be directly distributed to participants at the end of their courses to School of Health and University of Geneva School of Medicine

Data collection: Vaccination status, age, menopausal status, marital status, parity, tobacco consumption, medical records, geographic data, consulting-date and HPV-test result.

HPV tests: The HPV self-collection kit included a dacron swab, collection tube, instructions with explanatory pictures, consent forms and a participant demographic information. The

HPV analysis will be performed by Real-time PCR. Delay between sampling and lab processing will be noted.

Technical aspect: Written informed consent will be obtained by papier. All women will perform a self sampling for HPV testing using a simple swab with no medium. The results of HPV testing and sociodemographic data will be archived in a database.

Statistical analysis: The expected vaccination coverage in this population is about 50%. According vaccination status, 2 different groups will be formed vaccinated *vs* non-vaccinated). The cases of HPV infection (status HPV+) will then be calculated for each group and compared according to the vaccination status. The applied statistical tests will be McNemar's test for comparison.

Sample size: Sample size was obtained based on estimated prevalence of 6% of HPV 16/18 infection in the Swiss population aged less than 30 years. A total of 200 specimens per group would be needed to detect about an 85% reduction in HPV 16/18 prevalence (prevalence of 0.9% in the vaccinated population), given an 80% power and a two-sided significance level of 95% (based on representative data from England). We therefore estimate that a sample size of 400 women (200 in each group) will be adequate for the analyses.

Follow up: Participants will receive their results by e-mail directly via our colposcopy nurse. We will follow the HPV-positive participants every 6 months during 5 years to assess the evolution of their HPV status and the viral clearance. In order to do this, every 6 months they will receive a self-sampling sampling HPV kit at home, which they will return by mail to the HUG for analysis.

4. Statement regarding the relevance and potential contribution of the project to cancer control

Data from the registries will be used to assess the HPV prevalence of the pre-vaccine era and will be the basis for monitoring infection after post-vaccine introduction. This study will provide important data about the prevalence of HPV infection in a young and sexually active population of women and on the proportion of vaccinated and non-vaccinated young women.

Despite the impact of vaccine on invasive cancers is not expected until some decades after its extensive implementation, as the type-specific prevalence of HPV infection is very high in

young sexually active populations, the effect of a successful HPV vaccination program should be quickly detected by sentinel surveillance in this sub-population.

Monitoring the impact of the vaccination programs by detecting type-specific infection is important as it is the earliest anticipated change, and failure to detect protection from infection will indicate failure to prevent cancer in the subsequent decades and allow the implementation of appropriate changes in cervical cancer screening strategies.

This surveillance is required in order to document the expected gains in cancer prevention if there is appropriate population coverage. In our case, no data is available in Switzerland. Such surveillance would allow further studies to determine the duration of protection, long-term safety and actual impact on health-care cost consumption.

In this project, 400 young girls will know their statuses for HPV infection and will obtain information about this prevalent infection and offered sexual counselling. Those who test positive for HPV infection will be guided to a gynaecological consultation for adequate management.

By using self-sampling for HPV testing, we will demonstrate the potential benefit in terms of participation, lower cost and feasibility to determine the prevalence of infection. This method is much easier and cheaper than the current cervical cancer screening test used (Pap test), which requires a gynaecological consultation. The self-sampling could be used to increase the participation of young women in the cervical cancer screening programs and thereby increase the effectiveness of the overall program screening.

In conclusion, monitoring HPV prevalence among sexually active young women in different selected settings will provide an important early indication of HPV vaccine impact. These data will also contribute to add important information for cervical cancer screening.

5. Ethical issues

The investigators commit that this study will be conducted in accordance with the Swiss law, as well as in accordance with the recommendations of Good Clinical Practices (ICH E6-1996) and the Declaration of Helsinki (Fortaleza, October 2013).Before the study starts, the approval of the protocol by the Geneva Ethics Committee will be required, and all patients will give their written informed consent to participate in the study.

All the participants will be informed of the HPV results and a webpage containing information on the implications of having a positive result in women aged less than 30 years will be available. Information can also be obtained via our colposcopy nurse (a helpline will be available).

6. Financial consideration

This study includes no charge for the patients. Financial support was solicited for a 100% research nurse for 12 months period (FRS 135'000), to buy kit sampling HPV (FRS 60) and to Cepheid GeneXpert® System for HPV testing (equipment rental + Test cartridges) (FRS 40'000).

7. References

1.Petignat P, Faltin D, Goffin F, Billieux MH, Stucki D, Sporri S, et al. Age-related performance of human papillomavirus testing used as an adjunct to cytology for cervical carcinoma screening in a population with a low incidence of cervical carcinoma. Cancer. 2005;105(3):126-32.

2. Bigras G, de Marval F. The probability for a Pap test to be abnormal is directly proportional to HPV viral load: results from a Swiss study comparing HPV testing and liquid-based cytology to detect cervical cancer precursors in 13,842 women. British journal of cancer. 2005;93(5):575-81.

3. Read TR, Hocking JS, Chen MY, Donovan B, Bradshaw CS, Fairley CK. The near disappearance of genital warts in young women 4 years after commencing a national human papillomavirus (HPV) vaccination programme. Sex Transm Infect. 2011;87(7):544-7. Epub 2011/10/06.

4. Donovan B, Franklin N, Guy R, Grulich AE, Regan DG, Ali H, et al. Quadrivalent human papillomavirus vaccination and trends in genital warts in Australia: analysis of national sentinel surveillance data. Lancet Infect Dis. 2011;11(1):39-44. Epub 2010/11/12.

5. Brotherton JM, Fridman M, May CL, Chappell G, Saville AM, Gertig DM. Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study. Lancet. 2011;377(9783):2085-92. Epub 2011/06/21.

6. Mesher D, Soldan K, Howell-Jones R, Panwar K, Manyenga P, Jit M, et al. Reduction in HPV 16/18 prevalence in sexually active young women following the introduction of HPV immunisation in England. Vaccine. 2013;32(1):26-32.

7. Hariri S, Bennett NM, Niccolai LM, Schafer S, Park IU, Bloch KC, et al. Reduction in HPV 16/18-associated high grade cervical lesions following HPV vaccine introduction in the United States - 2008-2012. Vaccine. 2015.

8. Drolet M, Benard E, Boily MC, Ali H, Baandrup L, Bauer H, et al. Population-level impact and herd effects following human papillomavirus vaccination programmes: a systematic review and meta-analysis. The Lancet Infectious diseases. 2015.

9. Arbyn M, Verdoodt F, Snijders PJ, Verhoef VM, Suonio E, Dillner L, et al. Accuracy of human papillomavirus testing on self-collected versus clinician-collected samples: a meta-analysis. The Lancet Oncology. 2014;15(2):172-83. Epub 2014/01/18.

10. Duke P, Godwin M, Ratnam S, Dawson L, Fontaine D, Lear A, et al. Effect of vaginal selfsampling on cervical cancer screening rates: a community-based study in Newfoundland. BMC Womens Health. 2015;15:47. Epub 2015/06/11.

11. Sancho-Garnier H, Tamalet C, Halfon P, Leandri FX, Le Retraite L, Djoufelkit K, et al. HPV selfsampling or the Pap-smear: a randomized study among cervical screening nonattenders from lower socioeconomic groups in France. International journal of cancer Journal international du cancer. 2013;133(11):2681-7. Epub 2013/05/29.

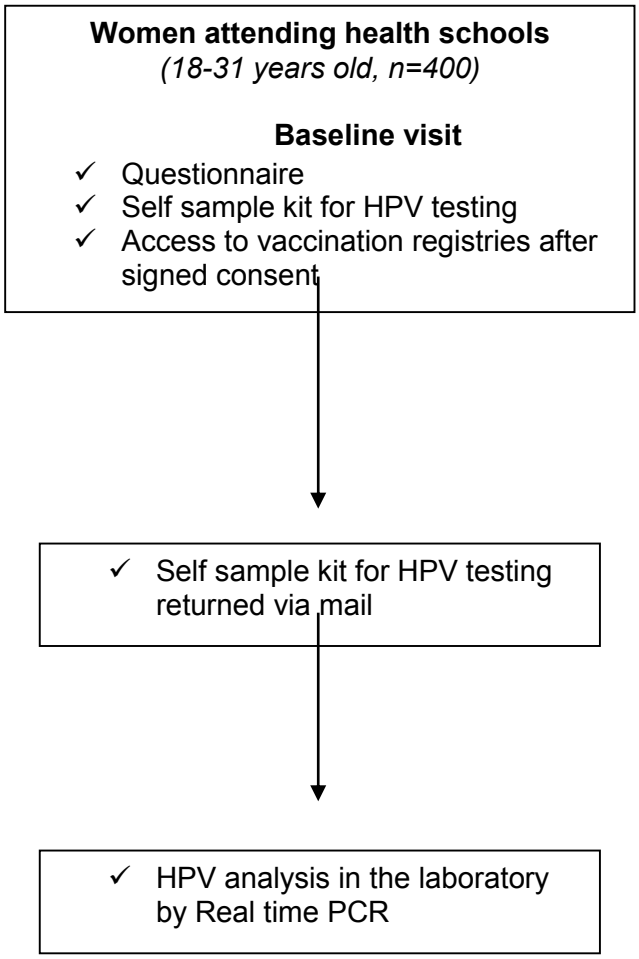
12. Tamalet C, Le Retraite L, Leandri FX, Heid P, Sancho Garnier H, Piana L. Vaginal self-sampling is an adequate means of screening HR-HPV types in women not participating in regular cervical cancer screening. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2013;19(1):E44-50. Epub 2012/11/10.

13.Lazcano-Ponce E, Lorincz AT, Cruz-Valdez A, Salmeron J, Uribe P, Velasco-Mondragon E, et al. Self-collection of vaginal specimens for human papillomavirus testing in cervical cancer prevention (MARCH): a community-based randomised controlled trial. Lancet. 2011;378(9806):1868-73

14. Snijders PJ, Verhoef VM, Arbyn M, Ogilvie G, Minozzi S, Banzi R, et al. High-risk HPV testing on self-sampled versus clinician-collected specimens: a review on the clinical accuracy and impact on population attendance in cervical cancer screening. International journal of cancer Journal international du cancer. 2013;132(10):2223-36

15. Catarino R, Jr., Vassilakos P, Stadali-Ullrich H, Royannez-Drevard I, Guillot C, Petignat P. Feasibility of at-home self-sampling for HPV testing as an appropriate screening strategy for nonparticipants in Switzerland: preliminary results of the DEPIST study. Journal of lower genital tract disease. 2015;19(1):27-34. Epub 2014/08/26.

Annexes: Flowchart of the study.



325
326
327